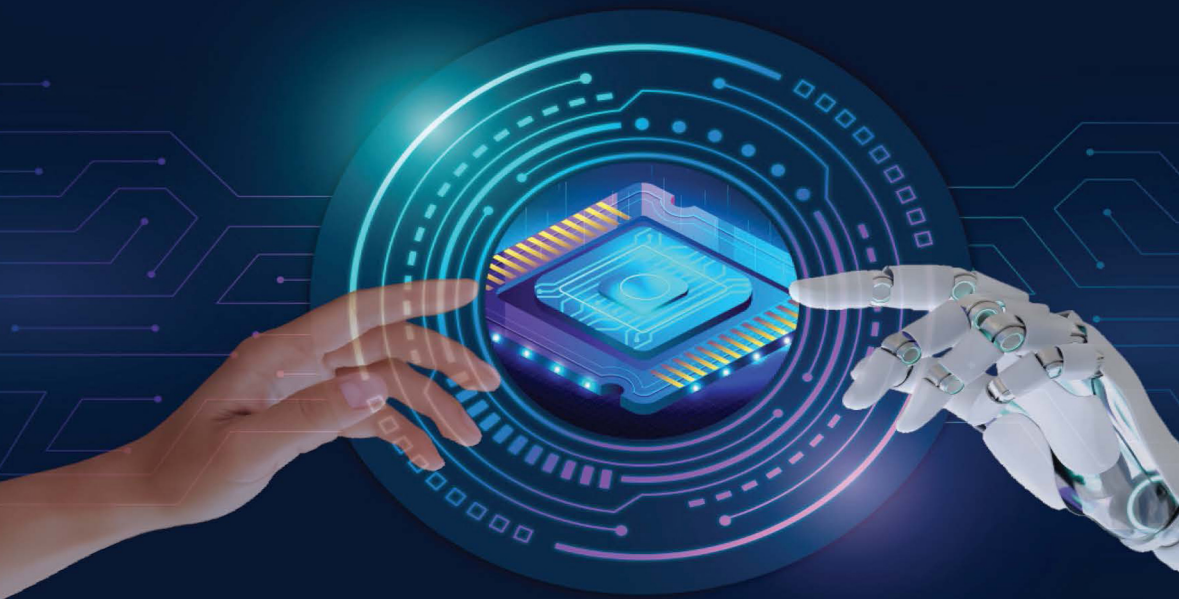
Nanosensors in Healthcare

Design, Applications, and Regulatory Aspects



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Design, Applications, and Regulatory Aspects

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Preface

Rapid, sensitive, precise, and timely diagnosis of a condition is a prerequisite for the initiation of an appropriate line of treatment. Nanotechnology has revolutionized the function of sensing. The global market of nanosensors is constantly growing with healthcare being a major area of application. Nanosensors offer a plethora of benefits in detection including point-of-care diagnosis, selectivity, sensitivity, low response time, multiplexed detection of analytes from complex matrices using small quantities of sample, etc. Their ultra-fine size also helps in implantation and portability. The applications of nanosensors in healthcare include diagnosis of diseases, therapeutic drug monitoring, monitoring biological phenomena, detection of drug abuse, and detection of biological warfare agents.

This book introduces the readers to the concept of nanosensors, the various nanomaterials employed in fabricating nanosensors, varied mechanisms of sensing via nanosensors, and their diverse applications in the healthcare field with suitable examples. There are chapters dedicated to the key mechanisms of sensing such as electrochemical, optical, magnetic, and ultrasound elucidating the principles and applications of each type. Further, there is a chapter on hybrid nanosensors which combine the attributes of two or more mechanisms of sensing. The book also touches on the regulatory aspects of nanosensors in healthcare and highlights the prospects of nanosensors in healthcare. The aim is to give the readers an overview of the possibilities and advances in the field. This book is a valuable resource for understanding nanosensors and designing them better to address the unmet needs in detection. It will foster more research in the healthcare field leading to innovative diagnostic tools for better management of a variety of diseases.

We are very grateful to all the authors for investing their precious time and energy in writing this book encompassing the design, applications, and regulatory aspects of nanosensors in healthcare. We wish to thank Mr. Viral Bakhai and Mr. Dhruv Gupta for the conceptualization and design of the cover page of this book.

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1

Introduction to Nanosensors in Healthcare

Priyanka Prabhu

Introduction to Nanosensors

The term sensor originated from the Greek word 'sentire' which means 'to perceive' (Khanna 2011). A sensor is a device that can detect and sense a particular signal. The signal may be biomedical, electrical, mechanical, optical, or physical. A sensor is a transducer that transforms a measurement into a signal carrying information (Kumar 2019). A nanosensor is defined as a sensor that utilizes a nanoscale phenomenon to exercise its function of sensing (Khanna 2011). Nanosensors utilize nanoparticles for sensing. Nanoparticles are defined as particles having at least one dimension in the range of 1–100 nm (Wang and Qu 2013). There are numerous examples of nanosensors in nature. Dogs have a strong sense of smell via receptors that sense nanosized molecules. Fish perceive tiny vibrations in the surrounding water via nanosensors. Similarly, many insects detect sex pheromones via nanosensors (Khanna 2011). According to the International Union of Pure and Applied Chemistry, a biosensor-based nanosensor is defined as a device that detects chemical compounds via specific biochemical reactions caused by isolated enzymes, immune systems, tissues, organelles, or whole cells, usually via thermal, optical, or electrical signals (Adam and Gopinath 2022). The introduction of nanomaterials into biosensors is the third generation of biosensors to enhance sensitivity and widen the scope of application (Kumar et al. 2023).

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Nanotechnology is contributing immensely to the development of sensors. Nanoparticles possess several benefits such as versatility in terms of size, shape, and composition, and the possibility of surface functionalization (Wang and Qu 2013). Recent times have witnessed an increase in the global market for nanosensors which has been realized through innovative design of nanosensors for medical diagnosis (Javaid et al. 2021). The estimated value of the global nanosensors market was around 760 million USD in 2023 and is forecasted to reach a value of 1512 million USD in 2033. Most of the market revenue is grossed from biosensors with a predicted Compound Annual Growth Rate (CAGR) of 6.6% by 2033. Healthcare is the topmost application of these biosensors with a CAGR of 6.3% in the forecast period from 2023 to 2033 (Saha 2023). Rapid, sensitive, and accurate testing is mandatory for early detection of medical conditions to enable timely treatment. Nanosensors permit real-time monitoring leading to immediate diagnosis of a medical condition (Saha 2023). Nanosensors have been designed with a limit of detection up to pico (10^{-12}), femto (10^{-15}), atto (10^{-18}), and even zepto (10^{-21}) molar scale (Munawar et al. 2019).

Nanosensors have immense potential to transform diagnosis enabling point-of-care (POC) testing. POC testing refers to testing or diagnosis performed at the bedside, or near the patient rather than in a traditional laboratory, generally performed by non-laboratory staff, and the diagnostic results are utilized to decide the correct treatment. POC has the advantage of quick generation of outcomes which can expedite treatment. A lot of emphasis is being put in recent times on patient-centric testing. There is a growing demand for the development of portable, handheld sensors enabling rapid POC testing of a variety of conditions. The design of POC nanosensors entails the integration of diverse areas of expertise (Singh et al. 2020). According to the World Health Organization (WHO) 'ASSURED' criterion, a POC sensor must be affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to the end user (Mauriz 2020).

This chapter (a) introduces the concept of a nanosensor; (b) elucidates the ideal characteristics of a sensor and how nanosensors help in achieving these desired attributes in a sensor; and (c) discusses the classification of nanomaterials employed in sensors, (d) elucidates different mechanisms of sensing via nanosensors and (e) explains the application of nanosensors in healthcare. The chapter also highlights the limitations of nanosensors which impede their clinical translation.

Ideal Characteristics of a Sensor

Certain attributes are desired in a sensor as outlined below.

Selectivity

Selectivity refers to the ability of the sensor to distinguish the analyte from other ingredients present in the sample matrix (Huang et al. 2021). Selectivity is essential to ensure specific detection of the analyte in a complex matrix such as blood or urine comprising several other components resembling the analyte (Bhalla et al. 2016, Tetyana et al. 2021).

Sensitivity

Sensitivity is the relationship between the change in analyte concentration and the intensity of the signal created by the transducer. It is desired that small changes in analyte concentration cause a signal. This feature helps to accurately detect trace amounts of analyte in a given sample matrix (Tetyana et al. 2021).

Accuracy

The accuracy of a sensor is its ability to give a result close to the actual or true value (Huang et al. 2021).

Repeatability

A sensor must have high precision. This means results of repeated measurements must lie close to each other (Huang et al. 2021).

Robustness

Robustness refers to a state wherein the sensor is minimally sensitive to factors leading to variation (either in the manufacturer's environment or during end-use) and aging at the lowest manufacturing unit cost (Heinold et al. 2021).

Multifunctional Nature

The sensor should be able to simultaneously analyse multiple analytes in an assorted matrix (Khanna 2011).

Cost-effectiveness

Large-scale fabrication of the portable sensor should be feasible so that disposable sensors can be provided at an affordable price (Bezzon et al. 2019).

Response Time

This parameter refers to the time taken for the sensor to reveal results (Tetyana et al. 2021). The short response time of a sensor enables quick analysis and facilitates timely action. This feature is extremely beneficial for the diagnosis of a disease so that the necessary mode of therapy can be immediately initiated (Khanna 2011).

Portability

Portability refers to the property of being light and compact enabling the sensor to be easily moved from one place to another. A portable sensor enables accurate and quick diagnosis in a resource-limited setting (Shin et al. 2021). It allows on-site diagnosis (Kaur et al. 2019).

Limit of Detection

This refers to the lowest concentration of the target analyte which can generate a measurable signal or response. It is desired that the sensor has the lowest limit of detection to detect trace amounts of analyte in a given sample (Tetyana et al. 2021).

Reproducibility

The reproducibility of a sensor refers to its ability to provide a consistent output in multiple experimental runs (Tetyana et al. 2021).

Stability

The stability of a sensor reflects its ability to resist any change in its performance over time on exposure to disruption by external factors such as temperature, humidity, etc. The stability feature is extremely important for sensors used in continuous monitoring (Tetyana et al. 2021).

Biocompatibility

Biocompatibility is desired in the case of implantable sensors and not in *in vitro* nanosensors. The properties of a sensor such as the nature of the matrix material, size, and shape govern its interaction with the immune system of the body and thus its compatibility (Ruckh and Clark 2014).

Eco-friendly Character: A sensor should be eco-friendly (Bezzon et al. 2019).

Advantages of Nanosensors

Nanosensors contain most of the attributes given above. Nanosensors possess certain advantages over their bulk counterparts, for example:

(a) Nanosensors have exceptional physical and chemical properties like surface effect, micro size effect, quantum effect, and macro quantum tunneling effect (Kumar et al. 2023).

(b) They possess a huge surface area/volume ratio that translates into enhanced sensitivity for the detection of a variety of molecules, even if the molecule is present in minuscule amounts and is as low as one part per billion (ppb) (Kumar 2019, Thangadurai et al. 2021).

(c) Conversion of bulk materials into the nanoform transforms their electrical, magnetic, and optical properties in a big way (Thangadurai et al. 2021, Wang and Qu 2013).

(d) Nanosensors offer high reactivity and show reduced response time (Kaur et al. 2019), thus enabling real-time detection (Chavan and Gilda 2021).

(e) Nanosensors are amenable to surface modification with ligands, including aptamers, antibodies, etc. that endow them with selectivity towards a particular analyte, especially in a complex sample matrix (Kaur et al. 2019).

(f) Their small size and light weight enable the portability and design of hand-held sensing devices (Khanna 2011).

(g) The ultra-small size also facilitates their implantation in the body in a minimally invasive manner (Gupta and Basu 2022).

(h) Nanosensors can be fabricated using an array of materials ranging from inorganic materials (gold nanoparticles, quantum dots, silver nanoparticles, magnetic nanoparticles, mesoporous silica nanoparticles (MSNs), and zinc oxide nanoparticles) (Parra et al. 2022, Pirzada and Altintas 2019, Que et al. 2021) to organic materials (polymeric nanoparticles and dendrimers) (Pirzada and Altintas 2019) and carbon-allotrope based materials (graphene, carbon nanotubes, and carbon nanodots) (Pirzada and Altintas 2019).

(i) Nanosensors can be fabricated in different shapes such as nanowires, nanofilms, nanotubes, etc. (Swierczewska et al. 2012).

(j) Nanosensors possess excellent cellular penetration and uptake (Arndt et al. 2020) which is useful for monitoring intracellular parameters or

markers such as glucose (Liao et al. 2019), oxygen (Zhou et al. 2019), pH (Zhang et al. 2022), singlet oxygen (Nath et al. 2021), etc.

(k) They also enable automated data acquisition (Saylan et al. 2022a).

(l) They require very small quantities of samples (Chavan and Gilda 2021).

(m) They have the potential to sense multiple analytes at once (Chavan and Gilda 2021). Complex diseases like cancer, osteoarthritis, and diabetes involve the analysis of multiple biomarkers for early and accurate diagnosis. In such cases, sensors that can detect multiple markers using a limited quantity of clinical samples are highly desired as they will have minimal errors due to fewer samples and increased throughput (Jarockyte et al. 2020). Examples of such multifunctional systems include nanosensors for multiplexed detection of cancer (Jarockyte et al. 2020) and nanosensors for simultaneous estimation of intracellular glucose and oxygen (Deng et al. 2019). Quantum dots are the most extensively explored photoluminescent nanoparticles and are one of the most common choices for different multiplex systems due to their ease of surface functionalization with a variety of ligands (Jarockyte et al. 2020).

Components of a Nanosensor

A nanosensor includes four key components as depicted in Fig. 1 (Gupta and Basu 2022, Sharma et al. 2021).

1. Analyte: Protein, antibody, carbohydrate, antigen, enzyme, etc. (Gupta and Basu 2022).
2. Sample: Any matrix such as blood, urine, saliva, sweat, semen, etc. (Das et al. 2023, Gupta and Basu 2022, Shandilya et al. 2020).
3. Transducer: A transducer may be optical, electrochemical, magnetic, or ultrasound to convert the recognized event into a computable signal (Hosu et al. 2019, Sharma et al. 2021, Sirsi and Borden 2014).
4. Detector: Enabling measurement of the signal (Gupta and Basu 2022).

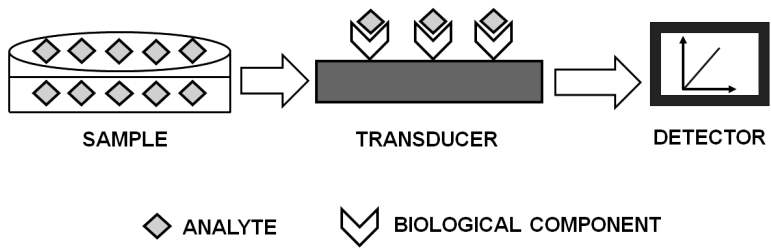

Fig. 1. Schematic representation of various components of a nanosensor. ⏎

Development of a Nanosensor

The development of a nanosensor involves multiple steps as depicted in Fig. 2 (Khazaei et al. 2023).

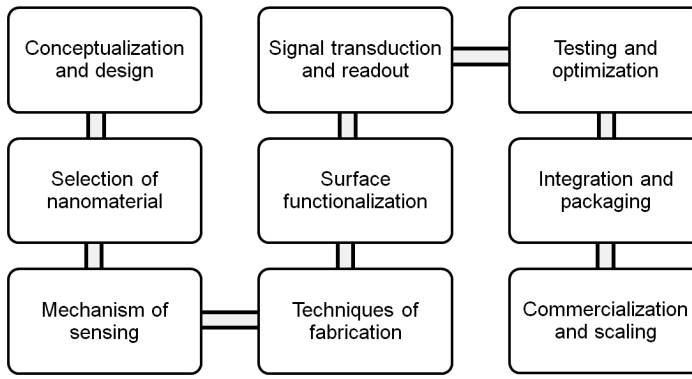

Fig. 2. Steps involved in the development of a nanosensor. ⏎

Conceptualization and Design (Khazaei et al. 2023)

The initial step in the development of nanosensors is the conceptualization which involves defining the purpose and application of the nanosensor. This step entails identifying the target analyte and deciding the desired sensitivity, selectivity, and operation parameters. The sensor design is then developed after considering suitable nanomaterials, transduction mechanisms, and fabrication techniques to fulfill the intended purpose.

Selection of Nanomaterial (Khazaei et al. 2023)

The nanomaterial used for the fabrication of the nanosensor is chosen based on its sensing ability, compatibility with the target analyte, stability, and ease of fabrication.

Mechanism of Sensing (Khazaei et al. 2023)

Nanosensors may utilize various mechanisms such as optical, electrical, and magnetic, to sense and transduce the target stimulus into a quantifiable signal.

Techniques of Fabrication

The nanosensors may be fabricated using top-down (electron beam lithography and focused ion beam milling) or bottom-up (chemical vapor deposition and self-assembly) approaches (Khazaei et al. 2023). The top-

down technique is a physical approach, utilizing unique size-reduction methods to decrease the original size. Bottom-up techniques are the most widely utilized techniques for fabricating nanosensors at the atomic or molecular level (Adam and Gopinath 2022).

Surface Functionalization (Khazaei et al. 2023)

Nanosensors mostly need surface functionalization to augment their sensitivity and selectivity towards the target analyte. Nanosensors may be surface functionalized with recognition elements specific to the target analyte such as antibodies, enzymes, DNA sequences, etc.

Signal Transduction and Readout (Khazaei et al. 2023)

The change in the sensor's properties post interaction of the nanosensor with the target analyte needs to be transduced and quantified. This entails the transformation of the physical or chemical change into an optical or electrical signal or any other measurable output.

Testing and Optimization (Khazaei et al. 2023)

Nanosensors are subjected to rigorous testing post-fabrication to assess their performance, selectivity, sensitivity, and response time. They may be exposed to known analytes under controlled conditions and the test results may be used to design iterative optimization processes to enhance the performance and reliability of the nanosensor.

Integration and Packaging (Khazaei et al. 2023)

The nanosensor needs to be incorporated into larger devices such as wearable devices, electronic circuits, or microfluidic platforms for practical usage post-development and optimization. Then the final product is packaged to ensure protection, stability, and easy usage in real-life scenarios.

Commercialization and Scaling (Khazaei et al. 2023)

This step aims to achieve bulk production and widespread usage. This entails manufacturing processes, quality control tools, and establishing supply chains to fulfill market demands.

Classification of Nanocarriers used as Probes for Nanosensors

Nanocarriers used as probes for nanosensors may be classified as organic, inorganic, and carbon-allotrope-based (Fig. 3) (Pirzada and Altintas 2019).

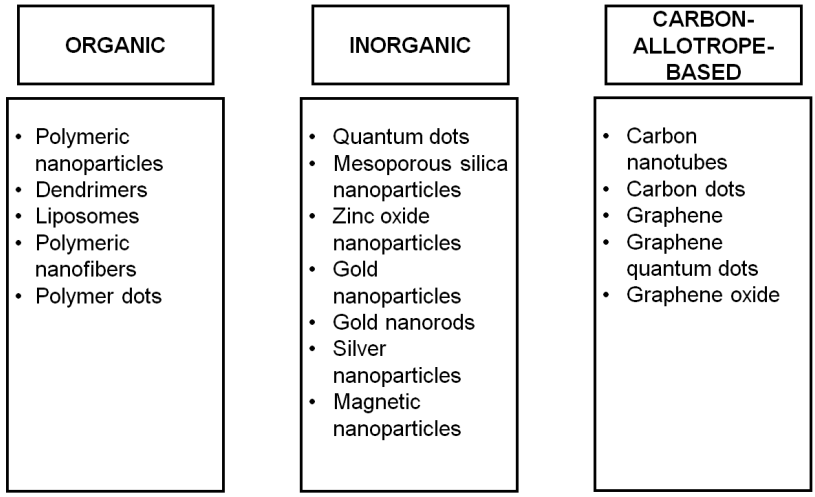

Fig. 3. Classification of nanocarriers used as probes in nanosensors. ⏎

Organic nanocarriers contain carbon, but inorganic nanocarriers do not contain carbon. Inorganic nanocarriers are more stable than their organic counterparts (Alshammari et al. 2023).

Organic Nanocarriers

These include polymeric nanoparticles, dendrimers, liposomes, polymeric nanofibers, and polymer dots (Deng et al. 2023, Li et al. 2023, Liu and Boyd 2013, Pirzada and Altintas 2019). Figure 4 depicts the various organic nanocarriers used in nanosensors.

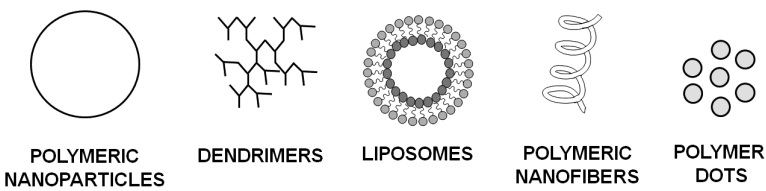

Fig. 4. Schematic diagram of organic nanocarriers used in nanosensors. ⏎

Polymeric Nanoparticles

Polymeric nanoparticles may be used in combination with metal nanoparticles, carbon nanotubes, and graphene to enhance their electrochemical sensing property (Ram and Jitender 2022). They may be doped with fluorophores and magnetic resonance imaging (MRI) contrast agents for detection (Gupta et al. 2020).

Natural polymers may be utilized for the fabrication of injectable nanosensing platforms as they contain homing peptides to augment stability in the blood stream and enhance retention in the body enabling real-time sensing.

Electrically conductive polymer composites may be utilized for fabricating wearable devices and cardiac implants as these are extremely sensitive and their electrochemical properties can be tuned with suitable agents.

Conductive polymers are endowed with the advantage of being less toxic than metals and hence are associated with a lower risk of immune rejection. They also offer great flexibility in design (Gupta et al. 2020). Examples of polymers that have been used in nanosensors include polyaniline for detecting biomarkers linked to cardiac failure and boronated poly (ethylene glycol) acrylate for *in vivo* imaging of thrombus (Gupta et al. 2020).

Dendrimers

Dendrimers are extremely controlled, synthetic, highly branched, monodisperse, spherical structures of 2–10 nm size comprising monomers originating from the core and sequentially extending to the periphery (Iftikhar et al. 2019). Examples of dendrimers include polyamidoamine, poly (propylene imine), etc. Various attributes of dendrimers make them an ideal transduction element for electrochemical immunosensors. Firstly, dendrimers have a plethora of peripheral chemical groups facilitating their stable attachment to the electrode surface. Further, these chemical functionalities can be used to connect with antibodies via covalent or non-covalent interactions. Secondly, dendrimers are nanoscale macromolecules with a permeable architecture posing a low barrier to the diffusion of electroactive compounds at the electrode surface. Dendrimers are also amenable to combination with other nanomaterials to fabricate hybrid systems (Sánchez et al. 2019).

Liposomes

Liposomes contain a phospholipid bilayer enclosing an aqueous cavity loaded with molecules of interest. Liposomes are most widely explored as optical sensors, although they also perform well as magnetic and electrochemical sensors (Sforzi et al. 2020). An array of molecules including fluorescent dyes, enzymes, electrochemical markers, etc., are encapsulated in liposomes for sensing. Liposomes are great signal amplifiers owing to the ability of a single liposome to bind with multiple signaling entities. Hence, liposome-based assays have revealed a low

limit of detection for various analytes such as hormones, viruses, bacteria, tumor markers, proteins, etc. The limit of detection is as low as picomoles/ml or femtomoles/ml (Liu and Boyd 2013).

Polymeric Nanofibers

Nanofibers are sub-micron-sized fibres with sizes in the range of 50–500 nm (Khanna 2011). Polymeric nanofibers may be fabricated using natural and synthetic polymeric materials (Horne et al. 2020). The huge surface area and porosity of nanofibers translate into enhanced sensitivity and response time. Electrospun nanofibers have been explored in electrochemical sensors for the detection of metal ions, biomedically relevant substances, and microbes (Halicka and Cabaj 2021). Nanofibers can be integrated with microfluidic devices for rapid, sensitive, and multiplexed analysis. They can also be combined with wearable devices such as smart watches and clothes to enable continuous monitoring of biomarkers. Three-dimensional printing is also being explored for the fabrication of nanofiber-based sensors with complex geometries and structures. The morphology of nanofibers is crucial in the performance of electrochemical sensors. The morphology can be optimized to augment sensitivity, selectivity, and response time (Iftikhar et al. 2023).

Polymer Dots

Polymer dots are nanoparticles consisting of hydrophobic semiconducting polymers with a volume or weight fraction of more than 50% and a diameter that is generally less than 50 nm. They have been explored for Forster Resonance Energy Transfer (FRET)-based sensing, fluorescence imaging, and photoacoustic imaging. Polymer dots have been explored for the detection of biomolecules such as the reduced form of Nicotinamide Adenine Dinucleotide (NADH), disease-related metabolites including glucose and phenylalanine, and tumor markers. However, future work in polymer dots needs to address the development of a large-scale, eco-friendly, and economical technique for the fabrication of polymer dots. Ultra-fine-size polymer dots of < 10 nm would facilitate biodistribution and quick metabolism for *in vivo* applications (Deng et al. 2023).

Inorganic Nanocarriers

These include quantum dots, MSNs, zinc oxide nanoparticles, gold nanoparticles, gold nanorods, silver nanoparticles, and magnetic nanoparticles (Parra et al. 2022, Pellas et al. 2020, Pirzada and Altintas 2019, Que et al. 2021). Figure 5 depicts the various inorganic nanocarriers used in nanosensors.

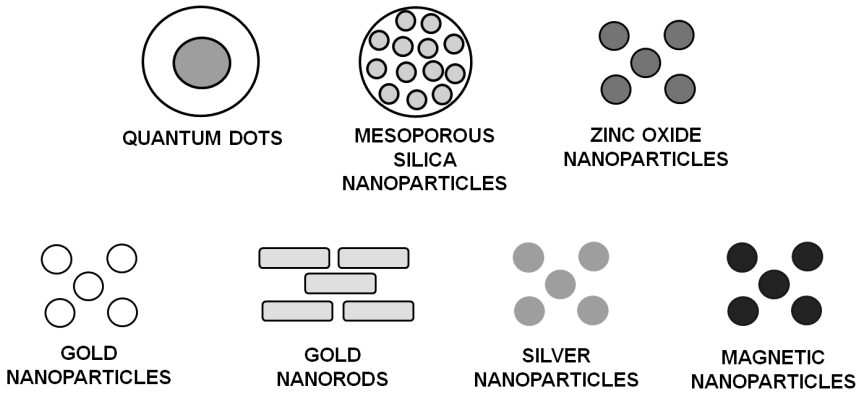

Fig. 5. Schematic diagram of inorganic nanocarriers used in nanosensors. ⏎

Quantum Dots

Quantum dots are semiconductors fabricated using elements from groups II and VI or groups III and V of the periodic table (Stanisavljevic et al. 2015). They are fluorescent semiconductors with a particle size of < 100 nm. They show exceptional optical and electronic properties because of their small size and huge surface area. Their emission wavelength spans from ultraviolet to the infrared. Cadmium-selenium (CdSe)/zinc sulfide (ZnS) core/shell quantum dots are generally used for biological applications (Singh et al. 2020). Quantum dots have been explored for theranostic purposes (combined diagnosis and drug delivery) (Matea et al. 2017).

MSNs

These are silica nanoparticles that have pore sizes in the range of 2 to 50 nm (Jafari et al. 2019).

They can be utilized in three different ways to develop sensors:

(a) Diagnostic probes may be loaded inside the pores to retain their optical properties or analyte binding properties. Their entrapment inside the pores may help to preserve their chemical and photochemical stability (Parra et al. 2022).

(b) Diagnostic probes can be covalently bound to the surface of MSNs (Parra et al. 2022).

(c) Dyes can be incorporated inside the pores and the pores sealed with molecular gates. These molecular gates open only in response to the analyte thereby releasing the entrapped dye (Parra et al. 2022).

Zinc oxide Nanoparticles

Zinc oxide is a semiconductor material with a wide bandgap and high excitation binding energy at room temperature (Que et al. 2021). The superior electrochemical activity and electron communication attribute of zinc oxide nanoparticles make them optimal for electrochemical nanosensors (Chaudhary et al. 2018). Zinc oxide nanostructures have been explored for the detection of glucose, urea, uric acid, dopamine, hydrogen peroxide, etc. (Sha et al. 2022). Zinc oxide nanostructures have also been explored for optical nanosensors based on SERS, Surface Plasmon Resonance (SPR), and fluorescence. Combining zinc oxide with metals such as Au and Ag enhances the efficiency of SERS and SPR-based nanosensors (Tereshchenko et al. 2016).

Gold Nanoparticles

Gold nanoparticles are conductive, have a huge surface area, and have distinct optical properties. They have a confined surface plasmon giving rise to a localized SPR (LSPR) effect. Hence, gold nanoparticles show a color change from red to yellow as their size increases from 100 nm (Pirzada and Altintas 2019). Gold nanoparticles are extensively utilized for electrochemical and optical nanosensors (Ram and Jitender 2022). Their plasmonic property renders them useful in SPR and Raman-based sensing (Holzinger et al. 2021). Multifunctional gold nanoparticles are being explored in the detection of various biomarkers for cancer, neurological disorders, and diabetes mellitus (Pirzada and Altintas 2019).

Gold Nanorods

Gold nanoparticles show a distinct LSPR band around 520 nm, whereas gold nanorods show two bands as they are 2-dimensional. The first band is a transverse LSPR band around 520 nm and the second one is a longitudinal LSPR band around higher wavelengths of 650–950 nm or 1000–1350 nm. The position of this longitudinal LSPR band can be programmed by changing the aspect ratio of gold nanorods. Hence, they are suitable for LSPR-based sensing (Pellas et al. 2020).

Silver Nanoparticles

Silver nanoparticles possess excellent electrical conductivity and hence are ideal for electrochemical detection. They are superior to gold nanoparticles with respect to electrical properties and are more cost-effective. The color of silver nanoparticles is governed by their size due to LSPR. Their optical

properties depend on the extent of aggregation, size, and shape. Silver nanoparticles are widely used in SERS-based sensors. Silver nanoparticles have been utilized for the detection of pharmaceutical and narcotic drugs, simultaneous detection of multiple breast cancer biomarkers, detection of cholesterol, etc. (Pirzada and Altintas 2019).

Magnetic Nanoparticles

They show optimum performance at sizes of 10–20 nm owing to supermagnetism (Rocha-Santos 2014). Examples of superparamagnetic nanoparticles include Fe_2O_3, Fe_3O_4, FePt, etc. Magnetic nanoparticles may be used in optical, magnetic, and electrochemical sensing. They have been explored for cancer detection, pathogen detection, and detecting biomarkers for asthma and cardiovascular disease (Pirzada and Altintas 2019).

Carbon-allotrope-based Nanocarriers

Carbon-allotrope-based nanocarriers include carbon nanotubes, carbon dots, graphene, and graphene oxide-based nanomaterials (Pirzada and Altintas 2019). Carbon-allotrope-based nanocarriers are endowed with an excellent blend of optical, electrical, and mechanical properties resulting in miniaturized sensors with low power consumption. These nanomaterials show great flexibility, thermal stability, electron mobility, and superior strength-to-weight ratio (Pirzada and Altintas 2019). Figure 6 depicts the various carbon-allotrope-based nanocarriers used in nanosensors.

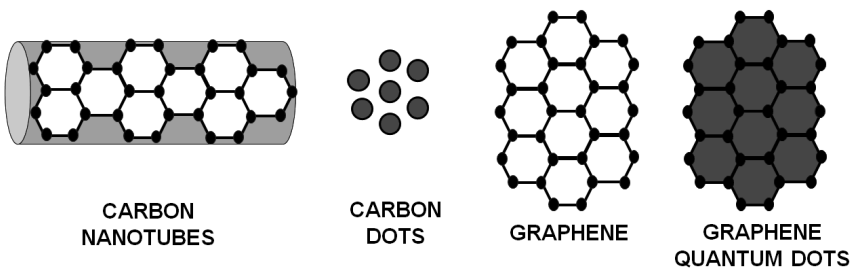

Fig. 6. Schematic diagram of carbon-allotrope-based nanocarriers used in nanosensors.

Carbon Nanotubes

Carbon nanotubes are hollow cylinders of graphite sheets with a diameter in the nanosize range (Bozal-Palabiyik et al. 2019). These are two-dimensional nanomaterials having sp^2 carbon units with several nm in diameter and

many microns in length. They can be single-walled or multi-walled (Abdel-Karim et al. 2020). They possess good electron transfer capacity and are ideal for electrochemical nanosensors (Kurbanoglu and Ozkan 2018). Carbon nanotube sensors can be fabricated in the form of textile-based sensors to record electrocardiography, electroencephalography, and electromyography signals (Rdest and Janas 2021). Carbon nanotubes may also be combined with metal nanoparticles for a synergistic effect with respect to sensitivity and electrical connectivity. Carbon nanotubes have also been explored in fluorescent optical nanosensors (Ferrier and Honeychurch 2021). Covalent and non-covalent surface modifications may be done to enhance sensitivity and selectivity towards target analytes and enhance the aqueous solubility of carbon nanotubes (Schroeder et al. 2019).

Carbon Dots

Carbon dots are spherical, biocompatible nanoparticles < 10 nm in diameter. They possess a sp^2 hybridized structure containing oxygen in various forms like (–OH), carboxylic acid (–COOH), and aldehyde (–CHO) groups (Mishra et al. 2018). Carbon dots are preferred for electrochemical sensors. They have also been used in optical sensors (Mansuriya and Altintas 2021). Bare carbon dots are weakly fluorescent, thus necessitating surface functionalization (Ding et al. 2014). Carbon dots have been explored for the detection of gamma amino butyric acid, glutathione, glucose, cytochrome C, etc. (Fan et al. 2022).

Graphene

Graphene is a 2-dimensional network of carbon atoms (Labroo and Cui 2013). Graphene has particular usage in electrochemical and fluorescence-based nanosensors. Graphene-based nanomaterials include graphene oxide (2-dimensional), graphene quantum dots (0-dimensional), and heteroatom-doped graphene quantum dots (0-dimensional). The heteroatoms may be nitrogen, phosphorus, and sulfur. Graphene oxide is in the form of a layered stack of nanosheets, graphene quantum dots are graphene oxide nanosheets cut into nanodots in the oxidation process (Cheng and Ou 2019).

Table 1 summarizes the salient features and challenges/drawbacks of various nanoparticles used in fabricating nanosensors.

Table 1. Summary of various types of nanoparticles used in fabricating nanosensors. ⏎

Nanoparticle type	Salient features	Challenges/drawbacks
Organic		
Polymeric nanoparticles	Ease of fabrication, flexibility, molecular imprinting ability, plentiful availability of biocompatible polymers for injectable and implantable nanosensors (Gupta et al. 2020)	Mechanical properties vary on changing temperature and humidity, prolonged retention of nanosensors in blood can cause surface modification leading to non-specific background signals (Gupta et al. 2020)
Dendrimers	Ample active peripheral groups enhance sensitivity by orienting recognition moieties such as antibodies on the sensor surface (Thakare et al. 2022)	Costly fabrication (Sk and Kojima 2015) and toxicity (Mishra et al. 2018)
Liposomes	• Good biocompatibility (Kumar et al. 2023) • Distinct structure allows the encapsulation of hydrophilic, hydrophobic, and amphiphilic agents (Chen and Wang 2015) • Amenable to surface modification (Chen and Wang 2015)	Poor stability, high cost of manufacture, and leakage of payload (Sawant et al. 2021)
Polymeric nanofibers	• Flexible and offer a huge surface area which translates into excellent sensitivity and low limit of detection (Asmatulu and Khan 2019) • High porosity and hydrophilic properties facilitate rapid ingress of analyte thereby reducing response time (Asmatulu and Khan 2019) • Amenable to surface functionalization (Asmatulu and Khan 2019)	Fragile and susceptible to damage compromising durability and robustness, and challenging large-scale fabrication involving difficult uniform and controlled arrangement of nanofibers (Khazaei et al. 2023)
Polymer dots	Good photostability, high luminescence quantum yield, and biocompatibility (Kumar et al. 2023)	Need to define their metabolism and long- term toxicity profile (Guo et al. 2018)

Inorganic		
Quantum dots	• Highly photostable (Knudsen et al. 2013) • Photoluminescence can be modified by changing size (Knudsen • et al. 2013) • Wide absorption (Knudsen et al. 2013) • High extinction coefficient and quantum yield (10–100 times brighter than organic fluorophores) (Knudsen et al. 2013) • Longer fluorescence lifetime than organic fluorophores (10–40 ns as compared to < 5 ns for organic fluorophores) (Knudsen et al. 2013) • Greater sensitivity in detection than organic dyes (Singh et al. 2020) • Amenable to surface modification with antibodies or DNA (Singh et al. 2020)	Toxicity and poor stability (Singh et al. 2020)
MSNs	• The porous structure offers good encapsulation of detecting probes inside and outside the pores enabling quick response time and low detection limits (Jafari et al. 2019) • Amenable to surface modification using ligands for targeting (Karaman et al. 2021) • Component amorphous silicon dioxide is categorized as Generally Recognized As Safe (GRAS) by the FDA (Karaman et al. 2021) • Good physical and chemical stability (Karaman et al. 2021) • Good optical transparency due to fine particle size (Jafari et al. 2019)	Scattered size distribution (Jafari et al. 2019)
Zinc oxide nanostructures	Excellent optical and electrochemical properties, and huge surface area (Que et al. 2021)	Challenging to precisely control the morphology (Que et al. 2021)
Gold nanoparticles	• Aggregation of gold nanoparticles causes a change in color visible to the naked eye, with a low limit of detection in the nM range (Wang and Qu 2013) • Amenable to surface functionalization (Shayesteh and Ghavami 2020), • Huge surface area (Abdel-Karim et al. 2020) • Good chemical stability and resistance against surface oxidation, and excellent biocompatibility (Bozal-Palabiyik et al. 2019)	Need to optimize large-scale manufacture and long-term stability under various environmental conditions (Si et al. 2021)

Table 1 contd. ...

...Table 1 contd.

Nanoparticle type	Salient features	Challenges/drawbacks
Gold nanorods	High refractive index sensitivity and tuneable longitudinal plasmon band by modifying aspect ratio (Cao et al. 2014)	Costly synthesis and difficult large-scale synthesis to achieve reproducible aspect ratio (Pellas et al. 2020)
Silver nanoparticles	• High thermal and electrical conductivity, cheaper than gold (Bozal-Palabiyik et al. 2019) • Excellent Surface Enhanced Raman Scattering (SERS) (Abdel-Karim et al. 2020)	Preserving the chemical and optical stability of silver nanoparticles during fabrication and surface modification is challenging (Alberti et al. 2021)
Magnetic nanoparticles	• Great sensitivity and low limit of detection, high signal-to-noise ratio, and small analysis time (Rocha-Santos 2014) • Economical production, physical and chemical stability, biocompatibility, and ecofriendly nature (Haun et al. 2010)	Long-term biocompatibility and toxicity need to be studied (Ali et al. 2021)
Carbon-allotrope-based		
Carbon nanotubes	• Excellent chemical, structural, mechanical, and electrical properties (Bozal-Palabiyik et al. 2019) • Single-walled carbon nanotubes show stability against photobleaching and intrinsic emission in the NIR region suitable for *in vivo* application (Rong et al. 2019) • High aspect ratio, excellent conductivity, great sensitivity, and amenable to surface modification with biomolecules (Kumar et al. 2023) • Fast response time and ultra-small size facilitate miniaturization (Khazaei et al. 2023)	Complicated and costly manufacturing involving exact manipulation and arrangement of discrete nanotubes (Khazaei et al. 2023)
Carbon dots	• Good resistance to photobleaching (Wang and Qu 2013) • Biocompatible and hydrophilic (Wang and Qu 2013) • Simple fabrication, chemically inert nature, and economical (Zhang et al. 2020) • Ultra-fine size, possess strong fluorescence in the infrared and visible region, excellent electron transfer capacity, amenable for surface engineering, and ecofriendly (Mishra et al. 2018)	Challenging to maintain properties over long periods (Mishra et al. 2018)

Graphene	• Low power usage, fast response time, and excellent sensitivity (Khazaei et al. 2023) • Ultra-small size facilitates miniaturization into wearable devices and the Internet of Things (Khazaei et al. 2023) • High mechanical strength, excellent thermal and electrical conductivity (Bezzon et al. 2019) • Graphene quantum dots exhibit biocompatibility, high water solubility, chemical inertness, stable photoluminescence, and easy surface functionalization (Cheng and Ou 2019) • Heteroatom-doped graphene quantum dots exhibit high chemical activity, higher fluorescence quantum yields, and effectively modulated performance of bandgap (Cheng and Ou 2019)	Difficult scale-up, prone to noise interference, stability issues due to sensitivity to humidity, and high cost (Khazaei et al. 2023)
Graphene oxide	Water dispersible, economical, biocompatible, realistic surface modification, and huge surface (Sargazi et al. 2022, Wang and Qu 2013)	Low fluorescence quantum yield (L. Zhang et al. 2018) and low electrical and thermal conductivity (Catania et al. 2021)

Mechanisms of Nanosensors

Nanosensors may be designed based on any of the mechanisms given below. Further, hybrid nanosensors may also be designed by combining two different mechanisms.

Electrochemical Detection

It is a rapidly growing field with the least effort in manufacturing techniques. It is popular because of its sensitivity, low cost, compatibility with miniaturization, and no requirement for pre-sample processing (Munawar et al. 2019). An important challenge associated with electrochemical sensors is the non-specific adsorption of unwanted substances present in complex biological matrices. This hampers the sensitivity, selectivity, and reproducibility of the sensor (Ferrag and Kerman 2020). Electrochemical nanosensors can be incorporated into smart phones and different analytical strategies to augment their sensitivity. Further, they enable multiplex detection in clinical specimens and serum samples with excellent selectivity and sensitivity (Hassan 2022).

The basic principles of electrochemical sensing include potentiometry, amperometry, conductometry, cyclic voltammetry, differential pulse voltammetry, square wave voltammetry, and electrochemical impedance spectroscopy (Das et al. 2023, Hassan 2022). The speed of electron transfer on the electrode governs the response time and accuracy of the electrochemical nanosensor. Nanoparticles exert an electrocatalytic effect thereby facilitating electron transfer and enhancing the response of the electrochemical sensor (Huang et al. 2021).

Typical materials employed in the fabrication of electrochemical sensors include carbon-based nanotubes, carbon dots, graphene, noble metals such as gold and platinum, and metal oxide nanomaterials including zinc oxide, manganese dioxide, and nickel oxide. These may be then modified with required enzymes for targeted detection (Das et al. 2023).

Electrochemical sensors have been widely explored and some of them have also been commercialized (Huang et al. 2021). Electrochemical nanosensors have been explored for microbial detection, toxin detection, diagnosis of viral infection, and cancer diagnosis (Hassan 2022). An electrochemical nanosensor utilizing copper oxide nanoparticles on a gold electrode has been explored for the detection of malaria parasites in clinical samples (Obisesan et al. 2019). Electrochemical sensors based on nanomaterials have been explored for the detection of drugs including paracetamol, ibuprofen, diclofenac, and dopamine (Chaudhary et al. 2023).

Electrochemical nanosensors are discussed in detail in Chapter 2.

Optical Detection

Optical sensors involve the interaction of the analyte with the receptor causing an optical phenomenon that is recorded and converted by the device. This signal is proportional to the analyte concentration (Halicka and Cabaj 2021). Light can interact with a material through which it passes in various ways such as absorption, reflection, refraction, scattering, and emission (Abdel-Karim et al. 2020). The basic principles of optical detection include colorimetry, fluorescence, SPR, SERS, and photoacoustic imaging (Cash et al. 2015, Harun-Ur-Rashid et al. 2022). The benefits of optical sensors include their small size and the fact that they allow direct and real-time detection (Halicka and Cabaj 2021). They are capable of multiplex sensing (Pei et al. 2020) and are also highly sensitive (Munawar et al. 2019). The disadvantages of optical sensing include interference from ambient light during their operation and poor stability of the indicator which may undergo leaching or photobleaching (Lobnik et al. 2012). Optical nanosensors may be fabricated using carbon-based nanomaterials, organic-based nanomaterials, inorganic-based nanomaterials, and composite-based nanomaterials (Kumar et al. 2023).

Optical nanosensors, based on the *in situ* formation of nanomaterials, eliminate the cumbersome preparation and purification procedures since they involve simultaneous detection of analyte and nanoparticle formation. Colorimetric nanosensors are mostly based on the *in situ* generation of gold and silver nanoparticles. *In situ* cadmium sulfide quantum dots, fluorescent silver nanoparticles, fluorescent silicon nanoparticles, and fluorescent copper nanoparticles are examples of fluorimetric nanosensors based on *in situ* formation (Guo and Zhao 2019). Optical nanosensors combining two optical imaging principles have also been explored for multimodal diagnosis. These combine the beneficial features of both optical imaging techniques (Li et al. 2017). Examples of multimodal diagnosis using optical nanosensors include nanosensors for dual colorimetric-fluorescent imaging (Hallaj et al. 2021, Zhu et al. 2021), nanosensors for dual fluorescence and SERS (Qu et al. 2017, Zheng et al. 2019), and nanosensors for dual fluorescence and photoacoustic imaging (Feng et al. 2020, Zheng et al. 2018).

Optical nanosensors have a variety of applications in healthcare such as the diagnosis of diseases (Alenichev et al. 2022, Shayesteh and Ghavami 2020), detection of molecules or phenomena indicative of disease (Garg et al. 2020, Shen et al. 2019), drug assays in pharmaceutical dosage forms (Azizi et al. 2019, Ding et al. 2018), detection of drug abuse (Masteri-Farahani et al. 2018, Masteri-Farahani et al. 2020), therapeutic drug monitoring and therapeutic efficacy monitoring (X.J. Zhang et al. 2018, Zhu et al. 2021), and theranostics (Feng et al. 2020, Ma et al. 2020).

Chapter 3 discusses optical nanosensors in detail.

Magnetic Detection

The benefit of using a magnetic nano-biosensor over an electrochemical or optical nano-biosensor is that the former creates less background noise because of the non-magnetic nature of the biological environment (Harun-Ur-Rashid et al. 2022). Current advances in MRI-based nanosensors have fostered a superior understanding of brain functions and metabolic processes. MRI is an optimal technique for drug monitoring because the nanoparticles can be spatially located irrespective of tissue depth (Rong et al. 2019).

Magnetic nanosensors may work either by recording magnetism or measuring the electric current. The ones that work on measuring electric current show loss in electric current post analyte adsorption because of change in the coating of magnetic nanoparticles which hampers energy transfer. Magnetic nanosensors that work on recording magnetism function on the principle of spin-spin relaxation time (T2). When these magnetic nanoparticles bind to the target tissue, they cause a decrease in the T2 levels of surrounding tissues facilitating sensitive detection (Lim and Ramakrishna 2006). Factors affecting the performance of magnetic nanosensors include the type of materials utilized whether paramagnetic, ferromagnetic, diamagnetic, antiferromagnetic, or ferrimagnetic (Issa et al. 2013), particle size (Issa et al. 2013), surface effects (Issa et al. 2013), and temperature (Issa et al. 2013).

Magnetic nanoparticles (superparamagnetic iron oxide nanoparticles) are widely used in tumor imaging (Kalubowilage et al. 2019). Magnetic nanosensors can detect biomarkers linked with cancer (Hosu et al. 2019), cardiovascular diseases (Ta et al. 2018), and infections (Eissa and Zourob 2020). Magnetic nanoparticles may be used for magnetically-guided drug delivery, magnetofection (gene delivery), and hyperthermia (application of an alternating magnetic field to reach higher temperatures of 40–43°C selectively at the tumor site) (Chang et al. 2018, Kalubowilage et al. 2019). Magnetic nanoparticles made from magnetite or maghemite are commonly used for biomedical purposes owing to their biocompatibility and stability (Schneider-Futschik and Reyes-Ortega 2021). Magnetic nanoparticles have also been explored as theranostic carriers. Antibody-functionalized fluorescent magnetic nanoparticles have been explored for targeted imaging and therapy of gastric cancer (Kalubowilage et al. 2019).

Certain issues challenge the clinical translation of magnetic nanoparticles for drug delivery. First, it is difficult to maintain magnetic nanoparticles in a 3-dimensional space under the influence of a magnetic field. Second, it is not possible to retain them at the target site after the removal of the magnetic field (Schneider-Futschik and Reyes-Ortega 2021).

Chapter 4 discusses magnetic nanosensors in detail.

Ultrasound Detection

Ultrasound waves or ultrasonic waves refer to elastic waves that have a frequency > 20,000 Hz and usually exist in solids, liquids, and gases (Ihara 2008). The ultrasonic sensor works on the principle of sound propagation and reflection by material in the ultrasonic frequency range (Stiawan et al. 2019). Ultrasound-based detection is convenient due to its mobility, non-invasive nature, and adjustable tissue permeation. It offers both surface and deep tissue imaging (Walker et al. 2020).

Gas-filled microbubbles are traditionally used for ultrasound imaging. However, they show short imaging time due to the diffusion of the gas into the neighboring medium. Hence, nanoparticles have been explored as ultrasound-based contrast agents (Walker et al. 2020). Further, for usage as theranostics (a combination of therapy and diagnostics), microbubbles often suffer from difficult chemical modification and poor drug loading capacity (Chen et al. 2017). A combination of silica and polymeric nanomaterials has been used to produce ultrasound contrast agents. This combination results in augmented mechanical strength, better imaging contrast, and ultrasound-induced drug release (Walker et al. 2020).

Ultrasound is a valuable theranostic tool that is useful to image drug carriers, induce drug release, and enhance drug uptake at the target tissue with superior spatial precision (Sirsi and Borden 2014). Ultrasound can induce drug release through internal cavitation resulting in mechanical damage to the drug carrier. Its chief advantage includes precise spatiotemporal control over drug release and enhanced drug transport into solid tumors as compared to other triggers such as pH, enzymes, and temperature. The intensity of ultrasound can be conveniently modified from low values of < 720 mW/cm^2 for diagnostic function up to 10^5 W/cm^2 for tumor therapy. The clinical translation of ultrasound-based theranostics requires the blending of enhanced imaging contrast, excellent encapsulation efficiency, and ultrasound-induced drug release in a single platform (Chen et al. 2017). Factors influencing the efficiency of ultrasound-induced drug delivery include frequency, intensity, mechanical index, and duration of ultrasound exposure (Tharkar et al. 2019). Ultrasound can enhance the uptake of nanoparticles within target tissue due to the mechanical energy that physically pushes the nanoparticles *in vivo*. This physical push propels the nanoparticles towards ultrasound-exposed tissues and causes localized uptake of nanoparticles. A combination of ultrasound and nanoparticles such as liposomes, micelles, solid lipid nanoparticles, and MSNs enhance anticancer efficacy synergistically. It solves the problems of inadequate nanoparticle uptake by cancer cells and low amount of drug released from nanoparticles and also enables targeted drug delivery to cancer cells (Tharkar et al. 2019).

Ultrasound-based nanosensors are discussed in detail in Chapter 5.

Hybrid Nanosensors

Nanosensors based on a single mechanism of sensing have their advantages and drawbacks. Thus, it is advisable to combine two or more sensing modalities to overcome the shortcomings of each (Rong et al. 2019). Examples of hybrid nanosensors include magneto-fluorescent nanosensors (Banerjee et al. 2019), MRI-luminescent nanosensors (Liu et al. 2014), colorimetric-electrochemical nanosensors (Guo et al. 2020), magnetic-electrochemical nanosensors (Hanoglu et al. 2022), etc.

Magneto-fluorescent nanosensors enable the separation of the target analyte from complicated samples and also enable analyte detection at trace levels (Xiong et al. 2022). Banerjee et al. developed a magneto-fluorescent nanosensor for quick and specific detection of *Staphylococcus epidermidis* and *Escherichia coli* in blood samples (Banerjee et al. 2019). MRI-luminescent nanosensors combine the excellent sensitivity of upconversion luminescence with the high resolution, non-invasive nature, and tissue-depth independence of MRI (Liu et al. 2014). Liu et al. developed a dual MRI-upconversion luminescent nanosensor for real-time monitoring of anticancer drug release from nanoparticles *in vitro* and *in vivo* (Liu et al. 2014). Colorimetric-electrochemical nanosensors combine the advantage of visual readout using the naked eye (colorimetry) with high sensitivity, convenient operation, easy miniaturization, and cost-effectiveness of electrochemical nanosensors (Guo et al. 2020). Guo et al. developed a dual colorimetric-electrochemical nanosensor for the detection of thrombin in complex matrixes (Guo et al. 2020).

Magnetically assisted electrochemical biosensors may also be designed. Electrochemical sensors need immobilization of recognition elements on the electrode surface. Magnetic sensors facilitate separation and pre-concentration of the analyte from a complex biological sample. Magnetic nanoparticles may be used as electrode modifiers for the immobilization of macromolecules including enzymes (Chang et al. 2022). Hanoglu et al. developed a POC system based on magnetic nanoparticle-based electrochemical sensing for early detection of colorectal cancer. The system enabled selective quantification of the methylated septin9 (mSEPT9) gene which is a diagnostic marker for early-stage colorectal cancer (Hanoglu et al. 2022).

Chapter 6 discusses hybrid nanosensors in detail.

Applications of Nanosensors in Healthcare

The rise in the number of senior citizens has created a huge demand for preventive medicine and self-health monitoring (Adam and Gopinath 2022). Nanosensors have incredible potential in various areas of healthcare

owing to their specificity, portability, amenability to automation, simplicity, quick analysis, and versatility (Garzón et al. 2019).

Nanosensors have a plethora of applications in healthcare as shown in Fig. 7.

Internet of Nanothings (IoNT) comprising interlinked sensors and actuators operating inside and/or around the human body is an emerging tool enabling monitoring and control of patients in real-time via the internet (Fig. 8).

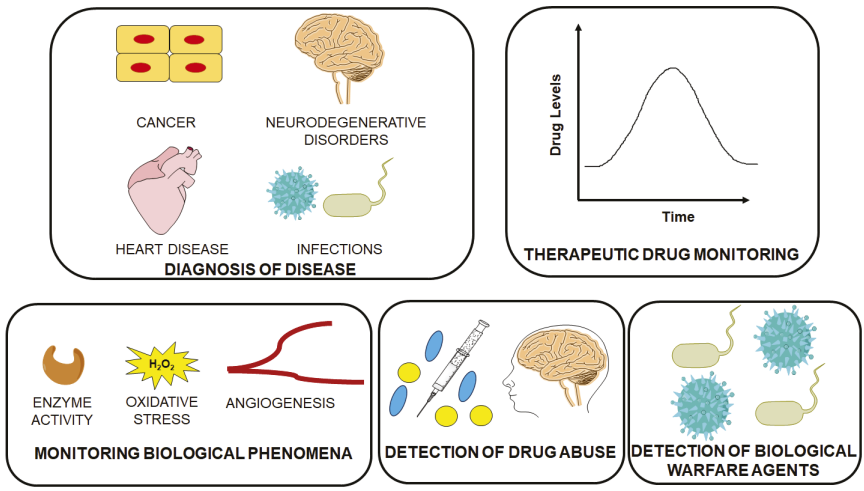

Fig. 7. Applications of nanosensors in healthcare. ⏎

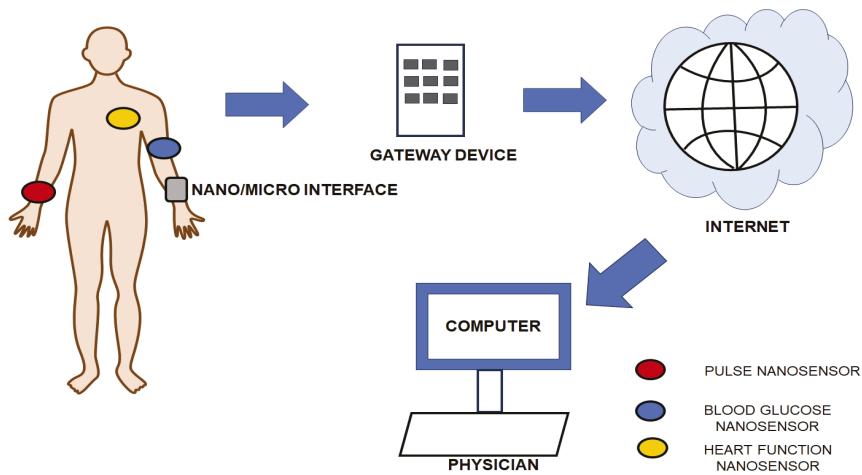

Fig. 8. Schematic diagram of IoNT. ⏎

IoNT also includes periodic drug delivery to the patient without any human supervision. The combination of sensors and actuators in the human body can collect vital information about the patient's heart beat, insulin levels, and so on (Khan et al. 2020). Wearable devices are a part of IoNT. IoNT can revolutionize healthcare due to the data capabilities, intelligent management, and superconnectivity of 5G (Verma et al. 2022). Parents can keep an eye on their child's addictive drug consumption. This can be done by installing nanosensors inside the child's body (Akhtar and Perwej 2020). The advantages of IoNT include enhanced sensitivity, excellent accuracy and precision, and superior energy efficiency. The snag associated with IoNT is the risk of cyber-attacks thus endangering security and privacy (Alabdulatif et al. 2023).

Diagnosis of Disease

A biomarker is defined as an indicator of a biological state or condition. A biomarker can be a protein, protein fragment, DNA or RNA, or a chemical produced by abnormal body cells. Disease biomarkers are molecular signatures of the physiological state of a disease at a specific time and hence are extremely crucial in early diagnosis and precise staging of the disease (Swierczewska et al. 2012). Nanosensors may be employed to detect abnormal levels of certain biomarkers in the body indicative of a particular condition; for example, increased blood glucose levels indicative of diabetes mellitus (Long et al. 2020), increased cholesterol and triglycerides indicating atherosclerotic cardiovascular disease (Farnier et al. 2021), and increased creatinine levels indicative of kidney disease (Younes-Ibrahim and Younes-Ibrahim 2022). They could also enable early diagnosis of a condition which can surely enhance management of the condition. For example, early detection of Parkinson's disease will help to counteract the disorder before irreparable harm has been caused (Adam and Gopinath 2022). Prostate-specific antigen (PSA) is extensively utilized for early diagnosis of prostate cancer. People with > 4 ng/ml of PSA in serum are likely to suffer from prostate cancer (Yang et al. 2018).

Conventional techniques used for diagnosis of infections typically are polymerase chain reaction, culture, and microscopy which are time-consuming, expensive, and require skilled personnel. On the other hand, nanosensors can be designed as POC diagnostic tests which would facilitate rapid diagnosis of infections even in developing nations (Noah and Ndangili 2019). Nanosensors have been developed for rapid detection of infections like hepatitis, malaria, HIV, tuberculosis, and COVID-19. They have also been explored for the detection of diabetes, neurodegenerative disorders, and cancer (Gupta and Basu 2022). Nanosensors are also useful in biopsy wherein they can be utilized to sample cells and protein from tissue to detect malignancy of the tumor in a non-invasive manner (Gupta

and Basu 2022). Nanosensors are also being explored for imaging of tumors for early detection of cancer. Metal oxide-based nanoparticles are functionalized with an antibody (which is specific for certain receptors overexpressed by cancer cells), which binds to cancer cells and enables MRI-based detection of cancer. For example, magnetic nanoparticles coated with antibodies against PSA are used for the diagnosis of prostate cancer (Gupta and Basu 2022).

Therapeutic Drug Monitoring

Therapeutic drug monitoring is significant in the administration of extremely potent drugs and drugs having a narrow therapeutic index. These include the anticancer drugs paclitaxel and methotrexate, the antiepileptic drugs carbamazepine and phenytoin, the opioid morphine, the immunosuppressant cyclosporine, and the cardiotonic digoxin. Therapeutic drug monitoring utilizes biological matrices such as blood, serum, urine, etc., for studying the pharmacokinetics of the drug and adjusting the dose accordingly. The conventional method of chromatography used to monitor drug levels is expensive and time-consuming. Nanosensors can be utilized to detect drug levels in patients in an easy, quick, and economical manner. Surface functionalization of the nanosensors is crucial to enhance sensitivity and prevent non-specific interactions. The main benefit of these nanosensors is they can be utilized at the patient's bedside and manipulated by the physicians. Optical nanosensors have been used widely to quantify a variety of drugs including anti-epileptics, antibiotics, anticancer drugs, etc. (Garzón et al. 2019). Electrochemical nanosensors have been utilized to quantify drugs like methotrexate, kanamycin, gentamicin, tobramycin, and doxorubicin (McKeating et al. 2016).

Monitoring Biological Phenomena

Monitoring intra-tissue biological activities is crucial in organ fabrication using regenerative medicine and tissue engineering strategies (Shafiee et al. 2019). Nanosensors have been explored for the detection of molecules such as glucose, H_2O_2, and matrix metalloproteinase, which are important for maintaining cell cultures and tissues. They can also monitor cellular physiology including ion fluctuations, enzyme interactions, and metabolite secretion. Electrochemical nanosensors offer superior spatial resolution and excellent sensitivity for intracellular monitoring in a non-invasive manner (Solaimuthu et al. 2020). Nanosensors are also useful in tracking various biological phenomena in the field of regenerative medicine and tissue engineering. They provide a non-invasive surveillance tool to support the processes of angiogenesis and cell signaling (Javaid et al. 2021). The design of such nanosensors requires proper consideration of

the tissue microenvironment and analytes pertaining to cell and tissue integrity (Shafiee et al. 2019).

Detection of Drug Abuse

Drug abuse is a global menace posing a threat to human life. Presently utilized methods for illicit drug detection are based on sophisticated instruments like mass spectrometry, high-performance liquid chromatography, gas chromatography, and so on. These methods involve the need for trained personnel, high cost, cumbersome sample preparation, and long assay time. The need of the hour is to develop hand-held nanosensors with excellent sensitivity and stability for on-field detection of illicit drugs such as morphine, cannabis, cocaine, etc. Numerous research efforts have been directed toward the development of optical and electrochemical nanosensors for the detection of illicit drugs (Dagar et al. 2022).

Barfidokht et al. designed a glove-based sensor consisting of flexible screen-printed carbon electrodes modified with a mixture of multiwalled carbon nanotubes and a room temperature ionic liquid, 4-(3-butyl-1-imidazolio)-1-butanesulfonate. The sensor uses the thumb for sampling and the index finger for sensing. The unified sampling and sensing procedure on the thumb and index fingers respectively offered quick detection of fentanyl (~ 1 min) in liquid and powder form and thus holds promise for on-site testing of doubtful samples (Barfidokht et al. 2019).

Detection of Biological Warfare Agents

A biological warfare agent may include an organism or its toxin and infectious cells, viral particles, and toxins capable of causing infection in humans and livestock. Examples of biological warfare agents include *Brucella abortus*, *Escherichia coli*, *Vibrio cholera*, *Bacillus anthracis*, *Clostridium botulinum*, *Yersinia pestis*, Ebola virus, etc. (Pohanka 2019).

Optical nanosensors based on carbon nanoparticles have been designed to detect 2,6-dipicolonic acid which is a biomarker of *Bacillus anthracis* spores (Pohanka 2019). Gold nanoparticles functionalized with an oligonucleotide complementary to the target DNA have been designed for the detection of *Brucella* species. The nanoparticles showed a very short analysis time from 1–10 min and a detection limit of pg/μL. Quantum-dot antibody conjugates have shown great success in the detection of protein toxins and viruses. Silica nanoparticles doped with fluorescent dye were used to detect calcium dipicolinate, a biomarker for *Bacillus anthracis* spores. Magnetic nanoparticles functionalized with antibodies have been used to detect *Bacillus anthracis* spores (Rowland et al. 2016).

Forms of Nanosensors

Nanosensors may be fabricated in the form of wearable devices, implantable nanosensors, and smart nanosensors/theranostics as discussed below (Fig. 9).

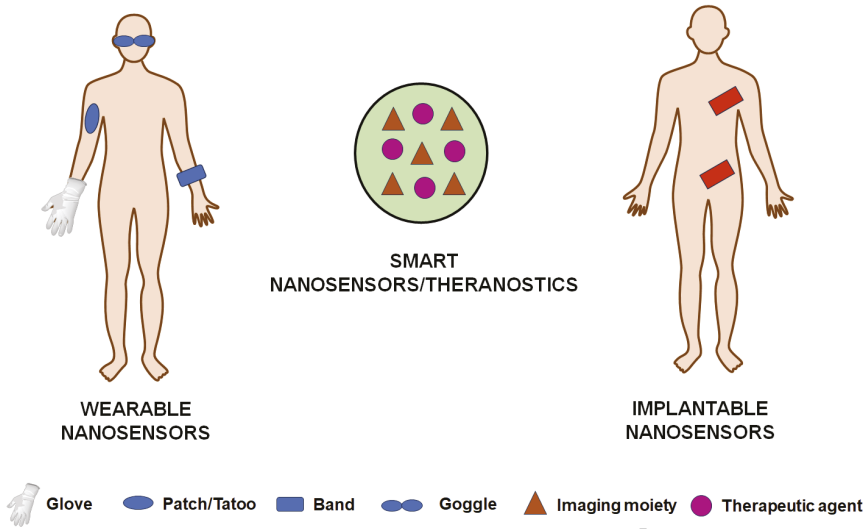

Fig. 9. Different forms of nanosensors.

Wearable Nanosensors

The nanosensing technology can be integrated with wearable devices for tracking health (Javaid et al. 2021). Wearable and flexible bioelectronics on plastics have garnered attention in healthcare due to their benefits of being light in weight and stretchable (Labroo and Cui 2013). These wearable devices can also be integrated with smart phones for user-friendly, POC testing (Saylan et al. 2022b). Several papers have reported the integration of electrochemical and optical nanosensors with a smartphone (Saylan et al. 2022b). Wearable nanosensors represent a non-invasive tool for diagnosis based on a wireless unit that conveys the information enclosed in the wearable device. The data from the device gets recorded for further storage in a database so that it can be analysed or processed to sense and foresee probable serious situations in the patient. They have also been developed to detect illicit drugs such as cocaine (Mahmud et al. 2019). Wearable nanosensors have profound applications in the fields of fitness, wellness, healthcare, and forensic science. The inclusion of chemical sensors into wearable platforms such as gloves, tattoos, etc., offers a convenient method of detection (Barfidokht et al. 2019). Detection of metabolites in sweat using wearable nanosensors has attracted significant research attention

as a part of non-invasive, personalized health monitoring. However, they are still in the nascent stage and have a long way to go as far as improvements in sensitivity, specificity, costly large-scale manufacture, durability, biocompatibility, reproducibility, and multiplexed detection of metabolites in sweat are concerned (Das et al. 2023).

There are certain challenges in the clinical translation of wearable nanosensors. The wearable devices need to overcome stability issues due to extended operation under uncontrolled conditions and biofouling from ingredients present in sampled biological fluids. Further, the wearable devices must maintain low power usage when providing continuous physiological monitoring. Data security is another crucial issue with wearable devices. There should be restricted access to a person's biomedical data (Kim et al. 2019).

Implantable Nanosensors

Implantable nanosensors have also been developed to enable analyte measurements *in vivo*. The complex and variable nature of the milieu *in vivo* necessitates robustness in the design of the implantable nanosensor with respect to stability, sensitivity, selectivity, etc. Implantable nanosensors could be immobile at a particular anatomical site in the body or they could be moving in the blood stream. They can be designed to produce electric, optical, magnetic, or acoustic signals in response to the analyte of interest (Ruckh and Clark 2014).

Implantable nanosensors would be useful for monitoring electrolyte fluctuations in patients having renal dysfunction. Implantable nanosensors offer the possibility of personalized medicine by providing continuous physiological tracking and monitoring of a patient's homeostasis and hence have immense potential to improve the quality of life in patients with chronic disease (Khan et al. 2020, Ruckh and Clark 2014). Implantable nanosensors may be employed for the detection and quantification of disease biomarkers associated with cancer (Williams et al. 2018).

Implantable nanosensors should be easily deliverable, removable, reversibly responsive, sensitive, specific, biocompatible, and biodegradable. It is a formidable task to achieve all these characteristics (Ruckh and Clark 2014). Tissue inflammation and foreign body response take over within a small period post-implantation (Vaddiraju et al. 2010). Fabrication of an implantable sensor which is easy to implant and easy to remove requires extensive miniaturization of all the components of the sensor. Such miniaturized sensors would cause less tissue damage and foreign body response. Nanosensors help to achieve this miniaturization attribute (Vaddiraju et al. 2010).

Smart Nanosensors/Theranostics

Another innovation in the field of nanosensors is the development of theranostic nanocarriers. These are nanocarriers endowed with dual functions of sensing or diagnosis and therapy. These nanosensors sense the condition and then release the therapeutic agent which could be a drug, genetic material, or a combination of two or more therapeutic agents. Theranostic nanocarriers have been designed for cancer, infections, inflammation, cardiovascular problems, wound healing, etc. (Shetty et al. 2019).

Theranostic nanocarriers also include smart nanosensors in association with implanted medical devices. The concept of smart nanosensors refers to using nanosensors that can not only sense an event but also respond to it to tackle the problem. An example of such a smart system is the integration of nanosensors with medical devices implanted within the body to track problems arising from the use of implanted medical devices. Prof. Thomas J. Webster and his team have developed this nanosensing strategy on orthopedic implants to sense if a bone cell or bacterium or an inflammatory cell has adhered to the implant. The mechanism of sensing the type of cell attached is based on conductivity. The sensor can communicate the performance of the implant in the body to a handheld device via radiofrequency communication. Thus, the patient is informed about the performance of the implant within the body. Further, the platform may also release an antibiotic or anti-inflammatory agent to counteract inflammation and bacterial growth on the implant. Additionally, it can be used to monitor the antibacterial efficacy or anti-inflammatory efficacy of the system. The smart nanosensor can further be extended to stents and catheters as well (Buntz 2013).

Marketed Nanosensors

Table 2 depicts the list of marketed nanosensors.

Limitations of Nanosensors

Although nanosensors possess a plethora of benefits in sensing, they also have certain limitations. Nanosensors may be prone to noise and interference wherein background signals, small changes, and impurities in the environment may affect the accuracy and reliability of the nanosensor (Khazaei et al. 2023). Nanoparticles may suffer from stability and reproducibility issues as they may show a drastic change in physicochemical properties on storage. The manufacturing process needs to be optimized to avoid variation in sensor properties within different batches (Khazaei et al. 2023). Cost is a major concern associated

Table 2. List of marketed nanosensors. ⏎

Nanosensor	Company	Salient features
HEATWAVE™	NANOCO™	• Quantum dot-based nanosensor for non-invasive quantification of bilirubin to detect liver function (455 nm), hemoglobin to detect blood oxygen levels (575 nm), and glucose to detect diabetes (1650 nm) (Abdellatif et al. 2022) • Pulses light through the patient skin and measures the absorption and scattering; on tuning to a particular molecule at a particular wavelength, the extent of scattering and absorption can be utilized to determine the concentration of the target molecule in patient blood (HEATWAVE™ Quantum Dots 2024)
VIVODOTS®	NANOCO™	• Used for the intraoperative mapping of pancreatic tumor tissues and preventing unnecessary removal of unaffected tissues (Abdellatif et al. 2022) • Involves biocompatible and fluorescent cadmium-free quantum dots equipped with selective cancer-targeting molecules (Nanoco 2017)
LiveOne	LiveMetric	• Worn on the wrist and provides real-time monitoring of blood pressure to enhance healthcare outcomes in cardiovascular disease • Combines microelectromechanical system nanosensors with artificial intelligence algorithms to accurately measure blood pressure • The device does not need any external calibration (LiveMetric 2022).

with the development and application of nanosensors. Their design and characterization entail sophisticated methodologies and instruments/equipments thereby escalating the manufacturing cost (Kaur et al. 2019). This poses a challenge to their use in resource-limited settings (Khazaei et al. 2023). Another grave issue associated with nanosensors is the potential toxicity of the nanomaterial. The nanosensors that are going to come in contact with biological systems have to be studied in-depth to confirm their safety. Similarly, nanosensors which may not come in direct contact with biological systems as such during their clinical application, but on disposal post usage can pose a threat to human safety, also need to be considered. Such nanosensors cannot be disposed of with general municipal waste. It is important to assess the toxicity of the nanosensor before it is commercialized and educate the public about its handling and disposal (Kaur et al. 2019).

Conclusion

Nanosensors have immense potential to transform the healthcare field in a colossal way. They can offer significant advances in the way diseases

are diagnosed and the time in which they are diagnosed. They can also be integrated with a therapeutic agent to design a smart nanosensor cum medicine that can not only sense a condition but also treat it. These nanosensors can be implanted in the body as small chips which would provide the physician an update of the condition of the patient. Numerous research efforts are being oriented toward the integration of nanosensing ideas with miniaturized portable platforms. An increase in the average human life span has led to a large geriatric population thus escalating the demand for wearable or portable devices for self-health tracking.

However, a few issues need to be resolved before nanosensors can be commercialized for various applications. There is a need to develop nanosensors that are biocompatible, consistent, cost-effective, and eco-friendly. Future research should also focus on the development of nanosensors for diagnosing disease using matrices such as urine, tears, and sweat to enable patient-friendly detection of disease conditions. Further, there is a need to develop standardized protocols for the characterization of nanosensors which would facilitate quality control of newly designed nanosensors and expedite their commercialization.

It is also imperative to note that the field of nanosensors is extremely interdisciplinary and involves the combination of expertise from diverse areas of physics, chemistry, biology, nanotechnology, material science, and engineering. Further, there is an urgent need to establish standardized protocols and regulatory frameworks for nanosensors. Fruitful collaborations between researchers, industry, and regulatory agencies can give rise to such regulatory guidelines. Also, academia, industry, and end-users need to come together to foster clinical translation of nanosensor-based diagnostics to improve human health. Nanosensors generate humongous data, hence, advanced algorithms, data analytics tools, and machine learning techniques have a role to play in extracting meaningful information from the enormous data.

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2

Electrochemical Sensors and Applications in the Field of Pharmacy

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Introduction

Sensors in simple term are devices which emit output signals for particular inputs provided by the physical environment. Accordingly, chemical sensors work by converting recorded data of analytes of interest into measurable signals (Fraden 2010). Electrochemical sensors come under a widely growing class of chemical sensors. Chemical sensors mainly consist of two active units; receptors which specifically interact with analytes of interest and transducers that convert the recorded responses into measurable signals (Hulanicki et al. 1991). Chemical sensors of all types have come a long way because their selectivity, specificity, sensitivity, small size, cost effectiveness, high automation and continuous online monitoring of signals has contributed to their wide applications (Barhoum and Altintas 2022, Arakawa et al. 2022, Wang 2016, Janata 2008, Mitsubayashi et al. 2019). The importance of accuracy in detecting analytes has led to the development of various innovations in sensor technology which can be applied to many areas of life.

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There are various types of chemical sensors including thermal, optical, mass chemical sensors, of which electrochemical sensors are more frequently utilized due to their lower detection limits, rapidness, reliability and cost effectiveness (Shetti et al. 2019). Due to their versatility, electrochemical sensors are widely explored in the field of agriculture to detect nutritional levels in soil (Chugh et al. 2022), in the food industry (Sharifi and Pirsa 2020), in monitoring environmental needs (Hanrahan et al. 2004), and in healthcare and diagnostic applications (Yunus et al. 2023). Electrochemical sensors as a technology have surpassed the traditional methods of analysis including chromatographic and spectrometric methods due to their low cost and portability (Karimi-Maleh et al. 2020). Electrochemical sensors have been studied considerably and based on the available literature, they hold the potential to be developed and utilized for commercial purposes.

This chapter focusses on electrochemical sensors and their pharmaceutical applications.

Electrochemical Sensors and Their Types

Electrochemical sensors include sensitive films and electrochemical converters, where the sensitive films identify the analytes, and electrochemical converters convert the chemically generated reactions into measurable electrical signals. The converter provides a quantitative or a semiquantitative data based on chemical reactions of analytes onto receptors which are placed in direct contact with electrodes (Hulanicki et al. 1991).

These electrode systems can be two or three-electrode based. The sensors based on the three electrode systems consist of reference, working and counter electrodes while the two electrode-based systems do not have counter electrodes. In general, three electrode-based systems are more commonly preferred where precise control and monitoring of working electrodes is required. In these systems, there is no limit to the amount of current being passed because the potential applied between working and counter electrodes is controlled via reference electrodes and the potential does not alter with time. Two electrode-based systems are used when the current generated is small and resistance produced by analyte solutions is very minute. Hence in most cases, three electrode-based systems find applications (Bard et al. 2022, Baranwal et al. 2022).

Figure 1 represents the general working principle of electrochemical sensors where the target analytes in sample solutions interact with receptors present on transducers, generating electrical signals which are recorded in the software.

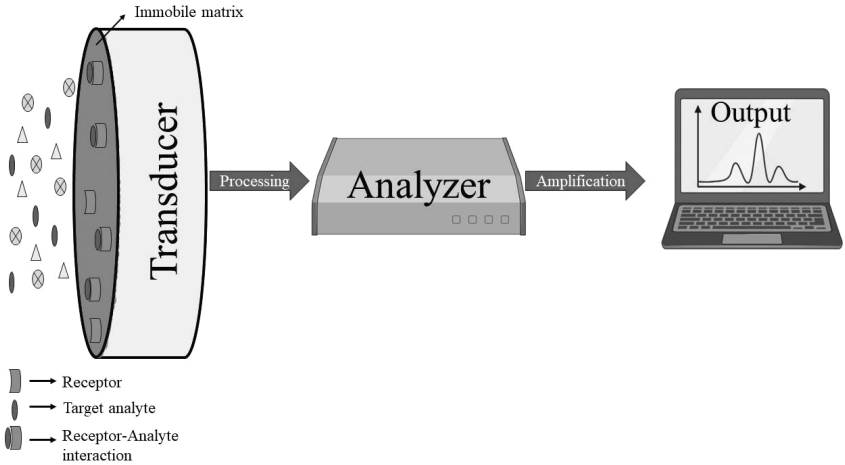

Fig. 1. General working process of electrochemical sensors. ⏎

Electrochemical sensors are categorized into three main types based on measurements, and include amperometric, potentiometric and conductometric or impedometric sensors. There are also other types of electrochemical sensors such as coulometric, electrogenerated chemiluminescent sensors, in addition to voltammetric sensors (Noor et al. 2024).

Table 1 depicts the various types of electrochemical sensors utilized in the detection of analytes.

Table 1. Electrochemical sensors used in the detection of various types of analytes. ⏎

Types of Analytes	Specific Receptor	Type of sensor	Reference(s)
Lead and Cadmium ions	Polyethylene terephthalate track-etched membranes (TeMs)	Potentiometric	(Zhumanazar et al. 2023)
Heavy metal ions	Bio and biomimetic receptors	Potentiometric/ Amperometric	(Stortini et al. 2020)
Vapors and Gas	Inert metals and enzymes	Potentiometric/ Amperometric	(Thiruppathi et al. 2021)
Proteins or small molecules	Ligands or aptamer-based protein detection	Potentiometric/ Amperometric	(Vestergaard et al. 2007)
DNA/RNA	Aptamer based protein detection	Amperometric	(Willner et al. 2007)

Potentiometric Sensors

In potentiometric type of electrochemical sensors, membranes or sensing surfaces produce battery generating potential proportional to analyte concentrations. Potentiometric electrochemical sensors are of three types: Coated wire electrodes (CWETs), Ion-selective electrodes (ISETs) and field-effect transistors (FETs). Selectivity of the electrodes to analyze particular species generally depends on the content of the membrane materials used in constructing the electrodes. This has resulted in the identification of a variety of analytes but the only limitation is the composition of ionophores and the dopants used in membranes matrices. ISETs can be of three categories based on the membrane types: glass, liquid and solid electrodes. ISETs are available commercially in companies like: Xylem, Metrohm, Orion, Hitachi to name a few. They are widely used in the identification of various ions like: cationic, ionic and organic species in waste water treatment, oil industry and various pharmaceutical industries (ElDin et al. 2021, Yoshinobu and Schöning 2021, Isildak and Özbek 2021). Wearable ion technology integrated with potentiometric ion sensors developed in recent years provides information on the physiological status of individuals based on their performance (Parrilla et al. 2019).

Another type of potentiometric devices are the pH electrodes, which have been extensively used for years. In these devices, thin layers of ion sensitive membranes made of glass are used to produce electrodes which are the most commonly used potentiometric devices available in various sizes and forms. In addition, there are also other types of potentiometric devices wherein the sensors are made of organic polymers or redox-active molecules that are used to check the pH. The glass membrane type of electrodes is used to check the pH of aqueous solutions. There is a need to improvise the type of measurement devices while determining the hydrogen ion concentration of non-aqueous solutions (Cho et al. 2022). CWETs are measurement devices in which the substrate of the conductors is coated with films of ion-selective polymeric membranes (polyvinyl chloride or polyacrylic acid) sensitive to the concentrations of electrolytes. These systems have an additional advantage in that they eliminate the use of reference electrodes and produce compact miniaturized systems for both *in vitro* and *in vivo* medical and biomedical monitoring of a variety of analytes. Ion selective FETs work as extensions of CWETs and integrate ion-sensitive membranes directly on the front side of FETs. The usefulness here is that small multiple sensors can be fixed on the front side of FETs, which can simultaneously identify multiple ions at a given time. Their small size allows *in vivo* determination of analytes (Stradiotto et al. 2003).

Amperometric Sensors

Amperometric type of electrochemical sensors are more commonly used due to their high sensitivity and accuracy, which make use of applied voltage as a stimulator for electrocatalysis, in turn generating an electric current which is directly proportional to the concentration of analytes of interest. This type of sensor controls the overall potential of these systems which consist of three electrodes wherein one electrode is the reference electrode. Here, reference electrodes maintain a constant potential as compared to the working electrodes where the actual reaction occurs. Developments in the fabrication of working electrodes have made possible the use of amperometric sensors in real sample analysis and an example of this discovery is the development of biosensors (Stradiotto et al. 2003). However, there is still a need for supplementary electrodes to maintain constant ionic strength, prevent the electromigration effect and lower the resistance offered by the solutions (Stasyuk et al. 2022, Emir et al. 2021, Hu et al. 2022).

Conductometric/Impedometric Sensors

Impedometric sensors are non-selective sensors and analyze the conductivity of systems using a particular sequence of frequencies. They generally rely on the principle that changing the ionic species concentrations causes a change in the conductivity of electrolytes. The electrodes can be either in direct contact with the solutions or shielded with a thin layer of glass. Although in contact mode the conductivity is good, there are higher chances of contamination of samples and that of electrode breaking. Hence, shielding the electrodes with thin layers of glass can eliminate the problem but the layer should be as thin as possible for better conduction. However, due to their non-selectivity, these sensors are not much preferred. However, modifying the surface of the receptors can improve their selectivity; for example, polymers can be used alone or in combination with conductors. Pyrroles were used to detect volatile amines but when used in combination with ClO_{4-} and tosylate, they can be utilized as -NH_3 sensor (Stradiotto et al. 2003, Janata et al. 1998, Janata Jiri 2009).

In the recent scenario considering their advantages, electrochemical sensors have turned the attention of scientists towards development and innovations in existing technologies and furthering their use in diagnostic, healthcare and analytical applications. Although, electrochemical sensors have wide applicability in various fields, this chapter highlights the applications of electrochemical sensors in pharmacy.

Applications of Electrochemical Sensors in Pharmacy

Electrochemical sensors have been identified since long as the desirable method for the identification of various genetic, environmental and pharmacological species not only because of their accuracy and sensitivity but also due their low cost, size and analytical speed. In order to improve the analytical performance of electrochemical sensors, a variety of nanomaterials with remarkable properties, including polymers, organic metals, metal oxides and carbon-based nanomaterials have been investigated in research, for more than twenty years. In order to improve the specificity and loading capacity of the electrochemical sensors, there is a need to modify the receptors (ligands, enzymes, antigen, antibody and aptamers) that can specifically and effectively identify the targets. Further, modification in the structures and shapes of the receptor surfaces can enhance the surface area and electrocatalytic activity which in turn can potentially improve test sensitivity. Electrochemical sensors are gaining popularity for novel applications such as single-molecule sensing, *in vivo* analysis, wearable technology and point-of-care diagnosis (Zhou and Kubota 2020, Monzó et al. 2015).

Electrochemical sensors offer several benefits, including high sensitivity for low limits of detection and quantification; lesser response times for flow and alert systems analysis; versatility in structure; electrode configurations and materials along with ease of use; low-cost equipment and integration into various analytical systems.

One of the best examples of the application of electrochemical sensors includes glucose monitoring wherein glucose blood sensor strips are available commercially which are both inexpensive and portable. This technique is based on amperometric type of glucose sensing device employing screen printed enzyme electrodes. They generate more than $5 billion in revenue each year (Skládal 1997).

One of the applications of electrochemical sensors is in therapeutic drug monitoring systems (TDMS) specifically used in conditions like epilepsy where the antiepileptic drugs are associated with considerable toxic effects, variable pharmacokinetic profiles and drug-drug interactions. Here, the therapeutic monitoring of drugs is required to improve the patient's quality of life and to minimize the risk associated with overdosing of drugs.

Figure 2 represents the use of drug sensors in therapeutic drug monitoring which serves as an efficient tool to improve the monitoring of drugs at a personalized level.

Biosensors offer unique benefits for environmental and biological research including:

- ease of data collection.

- measurement of analytes without prior separation from the sample solutions.
- high sensitivity that able to measure concentrations as low as ng/ml.
- cost effective, ease of application and high benefit ratio (Castillo et al. 2004, Chaubey and Malhotra 2002, Llorent-Martínez et al. 2011).

Biosensors mainly consist of biological components like enzymes, DNA probes, antibodies live cells, nanoparticles, electrodes and cell organelles. Further, the sensors are connected with transducers that convert the signals generated during chemical reactions between analytes and biological molecules into quantifiable output signals. The processing system subsequently converts these signals into forms that are readable.

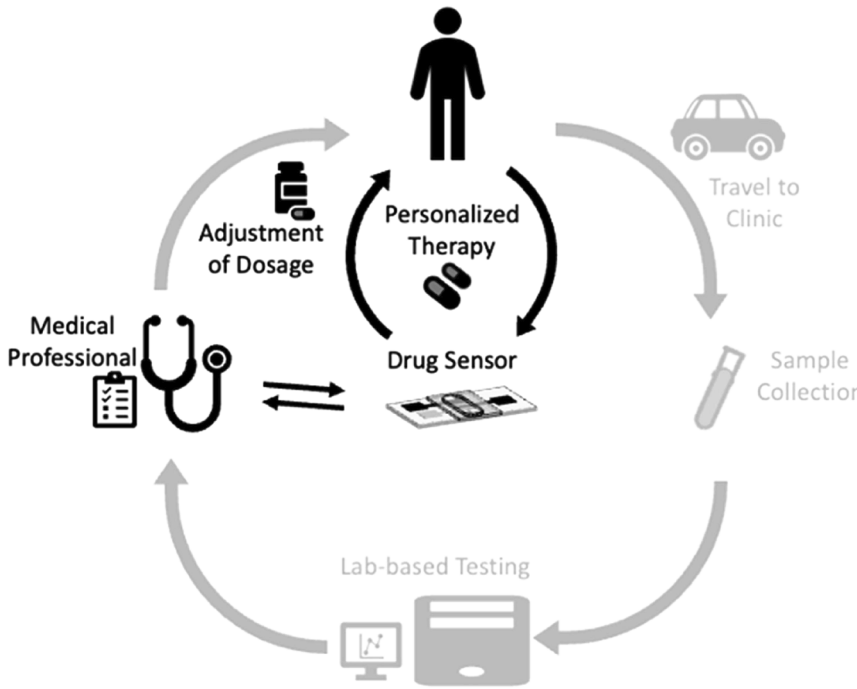

Fig. 2. Therapeutic drug monitoring using electrochemical sensors to detect drug concentrations in biological fluids [Reproduced from (Fu et al. 2023)]. ⏎

Nanomaterial Based Electrochemical Sensors

Nanomaterials have led to the development of innovative sensing systems. This section discusses various kinds of nanomaterials utilized in highly efficient and effective types of electrochemical sensors and biosensors to detect medicinal substances.

Carbon Derived Nanomaterials

Nanomaterials derived from carbon include carbon-nanotubes (CNTBs), graphene, diamond-like or crystalline diamonds have characteristic electrochemical properties, which has led to their wide applications in pharmacy. The potential of these materials in sensing applications is undeniable, as the unique carbon-derived nanostructures exhibit characteristics that are unknown in the bulk materials. This allows them to work with increased selectivity and sensitivity, as well as through wider temperature and dynamic ranges. Apart from carbon and platinum, gold has also been used as electrode material for electrochemical analysis since ages (Power et al. 2018, Adhikari et al. 2015). The more commonly used carbon-based nanomaterials are CNTBs and graphene and hence will be discussed in detail in this section.

Graphene and graphene-oxide based nanomaterials

Graphene, made of a single sheet of carbon obtained by sp^2 hybridization which is organized in hexagonal lattice, has unique electrical and structural properties (high surface area that makes it ideal for electrochemical analysis (Wanekaya 2011, Vedala et al. 2011, Liu et al. 2013). Graphene oxide (GO) has oxygen molecules as functional groups that can enhance the electrochemical sensitivity of certain analytes. However, the presence of these groups significantly lowers the conductivity of their surfaces (Lu et al. 2016) and hence, these groups can be reduced either electrochemically, chemically or thermally leading to the formation of vacant defects in them. Research indicates that the presence of these flaws can enhance the catalysis of many chemical compounds (Su and Loh 2013, Sun et al. 2012). Doping with certain elements which are metal free such as nitrogen can create certain unique electronic properties, making them valuable for sensing in electrostatic interactions. Additionally, heteroatoms can improve catalysis for different compounds (Kong et al. 2014). Nanomaterials derived from graphene like CNTBs can further be modified to improve selectivity and efficiency. These surface modified nanomaterials of graphene and graphene oxide can improve the stability and prevent agglomeration of deposited nanoparticles (Ravat et al. 2016, Wu et al. 2013.

Carbon Nanotubes (CNTBs)

CNTBs are composed of graphite which may be arranged as a single layer or multiple layers arranged parallelly. They are termed as single walled (SWCNTBs) and multi-walled carbon nanotubes (MWCNTBs) respectively. They are tube-like structures with size range 0.4 to 2.5 nm. These materials have good physicochemical properties which demonstrate

their use in the field of biomedicine (Hong et al. 2015). Similar to graphene, CNTBs can also be modified by surface functionalization which improves their catalytic properties and their sensing ability. In pharmaceuticals, CNTBs have been utilized for the adsorption of many organic compounds by utilizing their ability of electron transfer in chemical reactions (Camilli and Passacantando 2018, Bakshi et al. 2010, Pumera 2009).

The fundamental applications of CNTBs in pharmacy is in drug delivery for treating disease conditions like cancer and neurodegenerative diseases, and is used in gene therapy and applied for various diagnostics purposes. In drug therapy, CNTBs are used in such a way that the targeting drugs are attached either on their surfaces or fixed inside the nanotubes. These drug conjugated forms of CNTBs are further inserted into animal species either through the oral route or injections. They are directly targeted at the site of action using a magnetic conjugate approach which is driven by an external magnet. Further through the process of endocytosis, the drug CNTB conjugates are engulfed by the cells and release the drugs at target sites (Zhang et al. 2011, Zhang et al. 2010).

Figure 3 depicts the delivery of drugs using carbon nanotubes and uptake into cells.

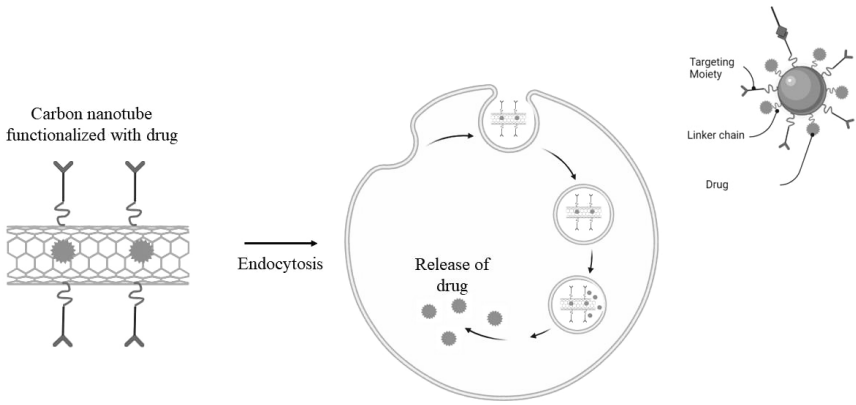

Fig. 3. Drug delivery from CNTBs and cell uptake via endocytosis. ⏎

Metal Based Nanomaterials

Metal nanoparticles are widely used for detecting pharmaceutical analytes due to their strong catalytic properties and small size. The journey of nanoparticles from molecular dimensions to nanostructures is mainly related to the physicochemical properties of desired metals, as well as, the interaction of nanoparticles with the environment. The dimensions, arrangement and surface of nanoparticles can be regulated by careful

fabrication of their surface and environmental conditions and further addition of capping agents and supramolecular interactions thereby playing an important role in production of nanoparticles (Sun and Zeng 2002, Bell 2003, Heiligtag and Niederberger 2013, Suryanarayana 2005). Metals such as gold (Au), platinum (Pt), palladium (Pd), silver (Ag), copper (Cu), cobalt (Co), including rare earth metals have been utilized for analysis (Abdel-Karim et al. 2020).

Electrochemical sensors based on metal nanoparticles hold tremendous potential for enhanced sensitivity and selectivity through controlling the amplification process. The development of metal and bio-functionalized nanoparticles including nanocomposites have captured the attention of many researchers directing them towards designing nanosensors. Several advanced analytical methods are being developed for environmental monitoring and food safety applications (Wang et al. 2010).

Noble metals such as Au, Ag, Pt, Pd, rhodium (Rh), ruthenium (Ru), osmium (Os) and iridium (Ir) possess an exceptional property of corrosion resistance and oxidation even at high temperatures (Lyon 2010). Metal-based nanoparticles are more selective to the analytes being studied than carbon-based nanomaterials. The interactions between metal nanomaterials and the target analytes can be improved by modifying the structural, morphological properties or the composition of metal-based nanomaterials.

Electrochemical sensors fabricated with gold nanoparticles are very popular in the market. The current scenario is the preference of green chemistry in developing gold nanoparticles. This is because gold nanoparticles developed using green chemistry are physiologically as well as catalytically stable, tactile and can also be applied in fabrication of wearable device technology. This process of green chemistry has an additional advantage that lesser chemicals are required, feasible large-scale production is possible and environmental safety is ensured because no harmful substances or chemicals are released. Another reason is the simplicity of the process and the requirement of less man power. These nanoparticles have applications in the field of medicine for drugs, proteins and gene delivery including diagnostic, theranostic and cellular imaging studies. Glass carbon electrodes are generally preferred in electrochemical sensors and the addition of gold nanoparticles makes this combination more stable and electrochemically active (Kalimuthu et al. 2020, Jadoun et al. 2021, Can 2020, Lee et al. 2020). Gold nanoparticles and methylene blue were mixed layer-by-layer to form laminated films on glassy-carbon electrodes capable of detecting human chorionic gonadotropins (HCG). The nanoparticles offered enormous surface area for loading the anti-HCG, making the immunosensor suitable for measuring HCG levels in blood or urine (Rizwan et al. 2019).

Polymer derived nanomaterials

In the last few years, conductive polymers have been used in synthetic compounds as electrochemical sensors for analytical purposes. Conductive polymers are desirable for their electroactive characteristics, high conductivity and characteristic behavior in the presence of electric fields (Uzun and Turner 2016). These conductive polymers are generally organic molecules including polyaniline (PAni), polypyrrole (PPy), polyacetylene (PAct) and polyfuran (PFu) to name a few (Namsheer and Rout 2021). Electrochemical sensors, fabricated using conducting polymers, are reported to have improved sensitivity and selectivity towards the targeted analytes. Recently, the concept of molecularly imprinted polymers (MIMP) has gained attention among scientists due to their ability to tailor interactions between sensors and analytes. This is especially beneficial for detecting analytes in complex compounds such as biological matrices where selectivity and fouling issues are the key concerns (Alqarni et al. 2020, Wong et al. 2019). MIMP includes imprinting cavities on polymer surfaces with template molecules which are detached later, while the polymers remain imprinted. The MIMP can detect target molecules by binding to functional groups in the cavities similar to how antibodies do. In a study reported by Hu et al. 2018, detected azithromycin in urine and serum samples with a detection limit of 2.3×10^{-11} mol L^{-1} wherein MIMP was utilized as the recognizing element and the detection was based on the principle of electrochemiluminescence (Hu et al. 2018). Lochab et al. utilized PPy as a conducting polymer for detection of chloramphenicol in water samples with a detection limit of 8.94 μgL^{-1} (Lochab et al. 2023). The performance of MIMP can be further improved by combining with carbon or metal-based nanomaterials.

Titanium Oxide (TiO_2) Based Nanomaterials

TiO_2 based nanomaterials are commonly used due to their additional advantage like chemical stability, compatibility with biomolecules, exceptional photocatalytic properties and their multipurpose applications. Also, they are stable in harsh conditions observed during their synthesis and later functioning of the nanomaterials and sensors. The characteristics of TiO_2 based nanomaterials can be further enhanced by combining TiO_2 nanorods or nanotubes functionalized with noble metal-based nanomaterials. Since the source is natural, the cost of production is also low as compared to those of noble metal-based nanomaterials (Chen and Mao 2007, Bai and Zhou 2014). Justin et al. investigated the photocatalytic activity of TiO_2 modified carbon-clay paste electrodes using cyclic voltammetry analysis to detect ascorbic acid. Here, the limit of detection and quantification identified was 0.732 μM and 2.440 μM respectively (Justin et al. 2023).

Electrochemical Sensors for Biomolecule Identification

Biomolecules are small size organic molecules which include hormones, nucleic acids, and enzymes that have important roles in regulating biological activity, transmitting genetic information, and catalyzing cellular activities (Knutson et al. 2020, Hannocks et al. 2019, Lu et al. 2019). Although, techniques such as gel electrophoresis, polymerase chain reactions and western blot are available for detecting biomolecules, all these processes are very tedious, time consuming, laborious and require expensive reagents (Asal et al. 2018, Wang et al. 2020).

Electrochemical sensors for detecting biomolecules at an early stage have been studied by researchers. Moonla et al. developed disposable screen-printed strips for electrochemical sensing with a purpose to measure β-hydroxybutyrate (HBT) in salivary fluid; HBT is one of the dominant physiological ketone bodies. This development enables the detection of HBT concentration more effectively after ingestion of commercially available keto supplements which proves its potential in varied healthcare and nutrition applications (Moonla et al. 2023).

Electrochemical Sensors for Detecting Viral Infections

Electrochemical biosensors are reliable, portable and cost-effective analytical instruments capable of reading turbid solutions with high sensitivity (Campuzano et al. 2017). DNA and RNA electrochemistry are used to diagnose viral diseases like hepatitis E, coronavirus, human immunodeficiency virus (HIV), influenza, bacterial infections, malaria, and Zika viral infections (Faria and Zucolotto 2019, Salimian et al. 2019, Shabaninejad et al. 2019, Cui et al. 2020, Chowdhury et al. 2019). These kinds of sensors can also be used as point of care tools which can be accommodated in clinics or at home due to their easiness to operate and low cost. As a result, extensive research has been reported describing ultrasensitive electrochemical biosensors that function exceptionally well for detection of infectious diseases (Cui et al. 2020). Table 2 enlists various viral infections detected using electrochemical sensors.

Ion Selective Electrodes (ISEs) for Diagnostic Applications

ISEs are generally used in analytical chemistry to determine electrolytes in fluids. Billions of measurements are performed annually worldwide (Burnett et al. 2000, Rutkowska et al. 2021). ISEs are promising candidates for pharmaceutical analysis due to their intrinsic advantages, which includes their ease of use, cost effectiveness, quick analysis, high precision and accuracy, low limit of detection (LOD), wide-ranging linearity, selectivity and in most cases, lack of pre-saturation of drugs from complex

Table 2. Different viral infections detected using electrochemical sensors. ⏎

Target	Type of electrode	Viral Infections	Analysis method	Reference(s)
DENV NS1 antigen	GCE	Dengue	CV and EIS	(Dutta et al. 2020)
RNA	SPCE	SARS-CoV-2	DPV	(Zhao et al. 2021)
ASFV p54	SPCE	Swine Flu	LAMP	(Yuan et al. 2023)
Ribavirin	GCE	Rabies, influenza (Type A and B) and HCV	ELP and PP	(Cetinkaya et al. 2023)
PED virus	GCE	PED	CV	(Li et al. 2023)

Abbreviations: DENV NS: Dengue virus non-structural protein; RNA: Ribonucleic acid; ASFV: African swine fever virus; PED: porcine epidemic diarrhoea; GCE: Glass carbon electrode; SPCE: Screen printing carbon electrode, HCV: Hepatitis C virus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, CV: Cyclic Voltammetry; EIS: Electrochemical Impedance Spectroscopy; DPV: Differential pulse voltammetry; LAMP: *In situ* loop-mediated isothermal amplification; ELP: Electropolymerization; PP: Photopolymerization

matrices (Crespo 2017). The basic nature of ISEs depends on the membrane materials which should be immiscible with the solvents and solid contacts. These membrane materials can either be solid or liquid electrolytes made of ionized or salt forms of acids or bases. These membrane electrodes (MEs) can be solid-state MEs, liquid ion selective membrane electrodes (ISMEs) or glass electrodes. All the mentioned types of electrodes have been utilized for detection of pharmaceutical compounds (Vytřas 1989). Since ISEs are mainly concerned with the activity of ions, they are mostly used in health care services (Coşofre and Buck 1993). Electrolytes can either be positive (sodium, magnesium, calcium and potassium) or negative (phosphate, chloride or bicarbonates) ions present in the human body and their imbalance often leads to dehydration, heart and kidney diseases. These conditions can be detected by ISEs using appropriate volumes of sample fluids (Yan et al. 2016). Boltia et al. developed green chemistry based ISEs for detection of dimenhydrinate and its metabolite along with cinnarizine in pharmaceutical and human plasma samples using solid contact sensor technology (Boltia et al. 2024).

Biosensors: Current Market Needs in Health Services

Biosensors in wearable health care devices are available that enable monitoring of the health and the environmental conditions of individuals wearing the devices. With the advancement of hardware technology, the functions of wearable devices have progressively expanded and now

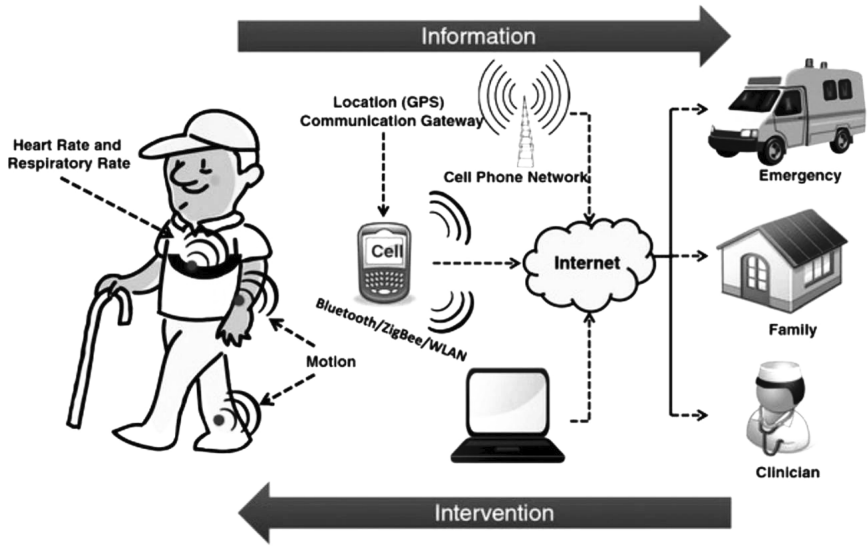

Fig. 4. Remote health monitoring using wearable technology [Reproduced from Smith et al. 2023].

include more diverse and precise forms of physiological indicators. This has contributed towards personalized health care systems. The principle with which these sensors work is that they transfer the physiological responses from the wearers to control units which then analyze and provide computerized feedback about the wearer's health. Figure 4 displays remote health monitoring using wearable technology.

Further, biosensors have also enabled detection of blood glucose in the presence of a variety of interfering molecules at varying temperatures. Marie et al. developed electrochemical sensors consisting of zinc oxide nanorods for detecting glucose as a low-cost, safe, accurate and rapid analytical technique.

Electrochemical Sensors for Environmental Monitoring

Environmental protection could see a radical shift in the coming years due to development in the area of electroanalytical chemistry. Electrochemical sensors and detectors have been utilized for environmental monitoring of toxic pollutants and this can be done on-site which means there would be o need to send samples to other clinics for analysis. Although, electrochemical sensors have a great deal of potential for environmental monitoring; their development for pollution management is still in its early stages (Moro et al. 2019). Various environmental pollutants including carcinogenic agents, inorganic compounds like metals, and pesticides as organic pollutants can be analyzed on site using electrochemical sensor

technology. It can also be used to detect water characteristics like acidity, alkalinity, presence or absence of chlorine, hardness and dissolved oxygen (Kanoun et al. 2021, Barhoum et al. 2023). Ansari et al. developed magnetic nanocomposites of cobalt ferrite electrospun nanofibres and graphene oxide for electrochemical detection of rutin in food products such as lemons, red apples, lime and orange juices (Ansari et al. 2020).

Bench-side to Commercialization

Going forward, it is critical to understand that continued advancements in the characterization of the effects of nanomaterials in biological and environmental media; improving the manufacturing processes of nanomaterials and their integration into the various components of sensors; miniaturization and cost reduction of electronic components are all necessary for the continued development of nano biosensors. Investments in research are now going toward creating data-driven procedures that will increase productivity and decision-making. Veridex's CellSearch® platform is a commercially successful nanosensing technique that uses ferrofluid reagent consisting of polymer coated magnetic nanoparticles that are targeted and can detect as few as 5 circulating tumor cells in 7.5 ml of blood.

Data driven and robust processes necessitate sensitive, selective and energy-efficient nanosensors that may be delivered via smooth integration across a variety of platforms. The National Network for Manufacturing Innovation (NNMI) offers research and manufacturing infrastructure where industry, government laboratories and academia collaborate to solve industry-relevant problems. This has emerged as a valuable resource for development and manufacturing of next-generation sensors in the United States.

The broader availability of nanoparticles in commercial products and processes highlights the ongoing need for development of techniques and tools capable of identifying and detecting manufactured nanomaterials throughout their life cycles. Other important concerns include large-scale fabrication, dependability, multiplexing for various targets or biomarkers, integration with microfluidics, and clinical sample demonstration. To guarantee dependability, the sensor signal needs to be dependable and resistant to parasitic influences. The immobilization of various receptors in nearby sensors gets more complicated as the size of individual sensors in arrays decrease. Finally, as sensing area decreases, capturing efficiency becomes an issue. Subsequent investigations would thus concentrate on items that are more affordable, user-friendly and efficient in order to facilitate their commercialization.

Conclusion

A wide range of nanosensors has been surveyed, categorized and discussed according to their working mechanisms and applications. Recently, nanosensors have found diverse applicability in the fields of medicine and pharmacy. Nanosensors can be used to solve many human problems and treat diseases as they can easily be adapted to the environment.

Finally, the challenges to researchers in the development of these important devices has always included practical difficulties of establishing reproducible but inexpensive methods and simple to use routine analyses equipment. With such a vast range of possibilities as described in this chapter, it is easy to realize the importance and significance of electrochemical sensors in the field of pharmacy.

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3

The Promising Potential of Optical Nanosensors in Healthcare

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Introduction to Optical Nanosensors

Nanotechnology has been applied to the field of optical sensors, enhancing their sensitivity (Bozal-Palabiyik et al. 2019). Optical nanosensors are defined as 'devices that transduce a chemical or biological event using an optical signal, having all dimensions < 1000 nm' (Aylott 2003). They sense variations in the properties of light like absorption, fluorescence, scattering, and refractive index arising from the interaction between an analyte and a receptor (Garzón et al. 2019).

A groundbreaking advancement in this domain was achieved in 1996 when Sasaki and their research group developed the first optical nanosensor capable of detecting pH changes. This sensor ingeniously employed polyacrylamide nanoparticles loaded with fluorescein dye (Sasaki et al. 1996). The concept of optical sensors hinges on exploiting diverse light-matter interactions to effectively sense and quantify molecules for an array of applications. Typically, an optical sensor comprises three key components: (a) a light source responsible for producing electromagnetic waves, (b) a sensing platform where the crucial light-matter interactions

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transpire, and (c) a detecting element adept at recognizing and quantifying spectral shifts arising from analysis of analyte-light interactions (Law et al. 2020).

Optical sensors may be based on different optical principles (absorbance, reflectance, luminescence, fluorescence), spanning different regions of the spectra such as ultraviolet (UV), visible, infrared (IR), and near-infrared (NIR), and permitting the measurement of the intensity of light and other associated properties, like lifetime, refractive index, scattering, diffraction and polarization (Lobnik et al. 2012). Optical nanosensors fabricated using carbon-based nanomaterials, organic-based nanomaterials, inorganic-based nanomaterials, and composite-based nanomaterials have been explored in the past (Kumar et al. 2023).

Optical nanosensors have several benefits over electricity-based sensors including selectivity, immunity to electromagnetic interference, and safety when working with explosive and flammable analytes (Lobnik et al. 2012). Optical nanosensors also have the advantage of portability and can be miniaturized for integration into existing optical systems (Kumar et al. 2023). Optical nanosensors are endowed with high sensitivity due to the characteristic connections between the active sites of nanomaterials and light signals (Munawar et al. 2019). Optical nanosensors are also capable of multiplex sensing (Pei et al. 2020).

Some drawbacks of optical sensing include the fact that ambient light can interfere with their operation, and long-term stability maybe compromised owing to indicator leaching or photobleaching; there may be a limited dynamic range; and a mass transfer of the analyte from the sample into the indicator phase is mandatory to obtain an analytical signal (Lobnik et al. 2012).

Principle of Sensing by Optical Nanosensors

The basic principle of optical sensing lies in the interaction between light and matter. When light interacts with a material, several phenomena can occur, including absorption, reflection, refraction, scattering, and emission as depicted in Fig. 1 (Abdel-Karim et al. 2020).

The continuous assessment of an analyte through the optical technique can be either by direct sensing or reagent-mediated sensing. Direct sensing involves substances that show intrinsic optical properties of absorption or fluorescence and reagent-mediated sensing involves a reagent that reacts with the analyte to produce a product having optical properties in the desired wavelength region (Qazi et al. 2012). The most widely used techniques in optical sensing are based on the absorption or emission of light (Lobnik et al. 2012).

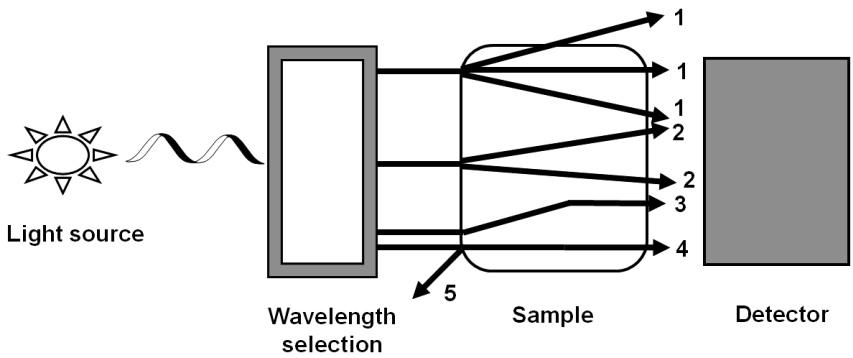

Fig. 1. Schematic representation of different light-material interactions. ⏎

Absorption-based Optical Sensors

Absorption-based optical sensors rely on the principle that certain materials absorb specific wavelengths of light. When light passes through or interacts with the material to be sensed, it undergoes a reduction in intensity at particular wavelengths, resulting in an absorption spectrum. The concentration or presence of the target substance can be determined by measuring the extent of absorption (Lobnik 2006). This principle finds applications in various fields such as environmental monitoring (e.g., gas concentration measurement) (Chen et al. 2021) and biochemical analysis (e.g., blood glucose monitoring) (Nguyen et al. 2023).

Reflectance-based Optical Sensors

Reflection of light occurs when light bounces off a surface and changes its direction. Smooth surfaces including glass mirrors and polished metal are ideal reflecting surfaces. There are two types of reflection: specular and diffuse reflection. Specular reflection refers to light reflected from a smooth surface at a fixed angle, whereas diffuse reflection is created by rough surfaces that reflect light in all directions (Fellers and Davidson 2024). An example of reflection-based sensing includes the concept of smart mirrors for non-invasive monitoring of human health. Smart mirrors combine the concept of reflection with electronic hardware and computer software. A normal mirror is converted to a smart mirror by placing a semi-transparent sheet of glass over a digital screen and linking the hardware to a computer with incoming data and a camera. A few research prototypes of smart mirrors include Wize Mirror and Medical Mirror. Wize mirror helps to estimate cardio-metabolic risk and anxiety

levels from anthropometric measurements of facial features. Medical Mirror enables people to monitor their vital signals daily. Computer vision captures the optical signal reflected off the person's face. The device can detect small deviations in reflections due to pulsating blood flow which provides information on the person's heart rate (Miotto et al. 2018).

Refraction-based Optical Sensors

Refraction-based optical sensors transform variations in refractive index into detectable optical information. This type of sensor can be utilized in biomedicine since cancer cells and viruses cause a statistical change in the refractive index. Plasmonic refractive index sensors based on metal nanostructures have been explored, out of which surface plasmon resonance (SPR) sensors have been commercialized. Localized SPR (LSPR) is observed in noble metal nanoparticles and the resonance frequency is related to the size, shape, and refractive index of the neighboring environment of the particles. A change in refractive index hence leads to a shifting of the LSPR frequency (Shen and Du 2021).

Scattering-based Optical Sensors

Scattering-based optical sensors work on the principle of change in the direction of light on interaction with the analyte (McCracken and Yoon 2016). Dynamic light scattering refers to changes in the intensity of scattered light on the μs timescale due to the diffusive motion of particles in solution. Static light scattering refers to measuring the average intensity of scattered light at different angles (Murphy 1997). Dynamic light scattering sensors detect the analyte based on the aggregation of nanoparticles functionalized with receptors of the target analyte. Alenichev et al. designed a nanosensor based on a combination of dynamic and static light scattering to detect *Aspergillus* galactomannan, which is a marker of invasive fungal infection. Gold nanoparticles functionalized with antibodies for *Aspergillus* galactomannan were used as the probe (Alenichev et al. 2022). Surface-Enhanced Raman Scattering (SERS) is a useful technique to study cellular processes at a molecular level (Kneipp et al. 2010). This technique is discussed in detail further in the chapter.

Emission-based Optical Sensors

These sensors utilize the principle of luminescence, wherein the energy of an electronically excited species is released in the form of light. There are two main types of luminescence: fluorescence and phosphorescence which vary with respect to the photophysical processes which take place in the molecule during excitation and emission. In fluorescence, the molecule returns directly to the ground state. As a result, the lifetime of

the fluorescence normally occurs over tens of ns (10^{-9} to 10^{-7} s), and the lifetime of the phosphorescence occurs over much longer periods (ms; 10^{-5} to 10 s). In certain cases, the analyte itself is the luminophore, whereas in some cases the analyte may quench the luminescence of the luminophore (Cajlakovic et al. 2006). Fluorescent nanosensors are extremely useful in monitoring sensitive biological reactions and detecting very low analyte concentrations (Chandra et al. 2020). They are endowed with high sensitivity and quick response time (Sargazi et al. 2022).

Interferometric Optical Sensors

Interferometry is an extremely sensitive tool for analyte detection (Khan et al. 2020). It measures the small change that occurs in the beam of light in its route of propagation. The change may be due to a change in the pathlength of the light beam, a change in the wavelength of light, a change in the refractive index of the medium through which the beam is traveling, or any blend of these three changes (Campbell 2008). Interferometers can sense refractive index changes of 10^{-7}, which corresponds to ppb concentrations of small molecules and pg/mL concentrations of toxins and proteins (Campbell 2008). An interferometric biosensor has been explored for the detection of *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*, which are the common bacteria responsible for nosocomial infections (Maldonado et al. 2020). Optical interferometric detection was also explored for the detection of specific Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) antibodies in serum and saliva (Murillo et al. 2021).

Different Types of Optical Nanosensors

Colorimetric Nanosensors

Colorimetric nano sensors involve the interaction of light with metal. In contrast to conventional colorimetric assays, colorimetric nanosensors do not require the usage of enzymes. Color is produced because of changes in absorbance owing to the optical properties such as the size of the nanoparticle, composition of the metal, nanoparticle morphology, and local environment. Colorimetric nanosensors are based on LSPR on the surface of conducting nanoparticles on photo stimulation because of the confinement of surface plasmons in the 2D-thin metallic layers. Gold and silver nanoparticles exhibit LSPR bands in the visible region of the electromagnetic spectrum. This forms the basis of colorimetric sensing. Gold nanoparticles have a higher extinction coefficient than organic dyes which translates into excellent sensitivity in the nM range. There are two chief colorimetric signal production mechanisms based

on the interparticulate distance or the morphology/size between metal nanoparticles. The distance-dependent color strategy is based on the cross-linking caused by the aggregation of neighboring particles. The morphology/size strategy is based on the growth and etching due to the modulation of the dimension and dielectric surrounding of metal nanoparticles. Colorimetric nanosensors have been explored for the detection of glucose, deoxyribonucleic acid (DNA), proteins, etc. The main advantage of using colorimetric nanosensors is the visual readout facilitating point-of-care diagnostics (Mauriz 2020). Colorimetry is also cost-effective (Bozal-Palabiyik et al. 2019), quick (Hai et al. 2018), and easy to operate (Bozal-Palabiyik et al. 2019). Nanocarriers such as metal nanoparticles, quantum dots, graphene and derivatives, and metal oxide nanoparticles may be used in colorimetric nanosensors (Wu et al. 2023).

Fluorescence-based Nanosensors

During fluorescence, an electron absorbs a high-energy photon, gets promoted to an excited state, and further returns to the original ground state with the fluorescence emission of a lower-energy photon. Stokes shift is the difference between the excitation and emission wavelength (Li et al. 2022). Fluorescent nanosensors either use the turn-on approach or the turn-off approach to track changes in fluorescence intensity. In case of the turn-on strategy, the fluorescence signal of the substrate is augmented by the exposure of the analyte to the substrate system enabling detection of the analyte through the modified fluorescence signal. On the other hand, the turn-off strategy involves quenching of the fluorescence signal of a luminescent molecule on exposure of the analyte to the quencher (Li et al. 2022).

Fluorescent nanosensors possess several benefits over traditional analytical instrumentational methods such as high-performance liquid chromatography, capillary electrophoresis, gas chromatography, etc., as they are biodegradable, economical, and eco-friendly. Fluorescence-based imaging offers a non-invasive method for real-time analysis (Sargazi et al. 2022). Fluorescence-based sensing is quick (Sargazi et al. 2022) and highly sensitive (Bozal-Palabiyik et al. 2019).

Fluorescent nanosensors may be based on organic fluorophores, up-conversion nanoparticles (UCNPs), semiconductor quantum dots, carbon nanomaterials, noble metal nanoclusters, etc. (Han et al. 2018). UCNPs are luminescent nanomaterials that have the property of emitting radiation of a shorter wavelength than their excitation radiation. They absorb light in the NIR region and emit photons of higher energy in the UV and visible regions. UCNPs have high photostability, long excited state lifetime, and low cytotoxicity (Arai and de Camargo 2021). Up-conversion is usually seen with doped transition-metal systems. However, it is also

seen with rare-earth doped solids and their combinations. It depends on the consecutive absorption of two or more NIR photons by the dopants (Jouyban and Rahimpour 2020). UCNPs mostly contain an inorganic host doped with Ln^{3+} ions (Chen and Zhao 2012). Different materials used in constructing UCNPs vary in intensity and emission color. UCNPs doped with Er^{3+} emit a green light in the 510–570 nm wavelength range and a red light in the 630–680 nm wavelength range. However, their maximum wavelengths and intensities are governed by the host lattice. Red emission is primarily seen in oxide-based lattices, whereas fluoride-based lattices exhibit green emission. Ho^{3+} doped lattices emit red and green light, Tb^{3+} doping shows green light, Tm^{3+} doping shows blue light, and Sm^{3+} doping shows orange light. Commonly used ions for doping are namely Nd^{3+}, Er^{3+}, and Yb^{3+}. $NaYF_4$ is a standard host lattice (Jouyban and Rahimpour 2020). A perfect host matrix should have low lattice phonon cut-off energies to diminish nonradiative energy losses in the intermediate states, thus enhancing the output of radiative emission. $NaYF_4$, $NaYbF_4$, $NaGdF_4$, $NaLaF_4$, $NaLuF_4$, $LiYF_4$, $LiLuF_4$, LaF_3, YF_3, GdF_3, GdOF, La_2O_3, Lu_2O_3, Y_2O_3 have been known as efficient upconversion host materials (Wu et al. 2015).

Organic fluorophores suffer from poor photostability and are challenging to prepare. In contrast, using semiconductor quantum dots entails the toxicity of heavy metal ions. Further, up-conversion nanoparticles have comparatively lower fluorescent quantum yields (Han et al. 2018). Conventional fluorescent probes such as quantum dots and carbon dots (CDs) are mainly excited by high energy radiation in the UV range (300–400 nm). However, UV light can also induce the emission of biological tissues and biomolecules, causing high background emission and reduced sensitivity levels (Arai and de Camargo 2021). Silica coating has been reported to improve the chemical stability of quantum dots and reduce the leaching of heavy metal ions in the body (Li et al. 2014). Quantum dots show size-dependent emission, good fluorescence intensity, and good resistance to photobleaching (Ankireddy and Kim 2015). CDs are promising probes for fluorescent sensing. They have a size of < 10 nm, are easy to synthesize, possess good chemical and optical stability, excellent quantum yield, are amenable to surface functionalization, are biocompatible, and are soluble in water (Azizi et al. 2019). Noble metal nanocarriers, including gold and silver nanoparticles, are also used as fluorescent probes. They possess controlled fluorescence and biocompatibility and can be utilized for targeted theranostic activity against cancer (Sargazi et al. 2022).

Ratiometric fluorescent sensing is based on analyte-induced changes in the intensity of two or more emission bands causing effective internal referencing with enhanced sensitivity for improved quantification (Lee et al. 2015). Ratiometric fluorescence sensing offers greater sensitivity and accuracy in analysis by decreasing the fluctuation in signal due to

environmental interference and amplifying the signal readout (Zhao et al. 2017). Ratiometric sensing results in an enhanced signal-to-noise ratio. Quantum dots, CDs, gold nanoparticles, silicon nanorods, silicon nanodots, and polymer-based nanoparticles may be used to develop ratiometric fluorescent nanosensors (Zhang et al. 2021).

Forster Resonance Energy Transfer (FRET) and internal charge transfer are examples of ratiometric fluorescent sensing strategies (Lee et al. 2015). FRET involves nonradiative energy transfer between two fluorophores owing to long-range dipole-dipole interaction (Stanisavljevic et al. 2015). FRET operates when the overlap between donor emission and acceptor absorption is more than 30%, and the distance between them is less than 10 nm (Safari et al. 2020). FRET sensors are popular for studying intracellular processes due to their enhanced sensitivity in angstrom distances (Solaimuthu et al. 2020).

Internal charge transfer platforms contain an electron-donating unit connected to an electron-accepting unit resulting in a 'push-pull' of Π electrons in the excited state. These are commonly employed for the detection of cations. When the cation interacts with the electron-donating platform, the electron-donating property of the platform decreases. This causes a blue shift in the absorption spectrum. On the other hand, when a cation interacts with the electron-accepting part of the platform, a red shift is seen in the absorption spectrum (Lee et al. 2015).

SPR-based Nanosensors

SPR-based sensors are optical refractometers able to measure changes in the refractive index of the medium at the SPR sensing surface. It is very tough for SPR-based sensors to detect low concentrations of analyte (below 1 pM) and low molecular weight analytes (< 8000 Da) (Zeng et al. 2014). The collective oscillation of conduction electrons in noble metals causes surface plasmon waves. These waves form an electric field that exponentially decays into the surrounding medium with a penetration depth of hundreds of nanometers. This field is sensitive to changes in the refractive index of the neighboring medium. The sensitivity of SPR is related to the excited electric field; the larger the electric field, the more sensitive are the SPR sensors to the change of neighboring medium (Zeng et al. 2014).

SPR sensors may be divided into two categories namely propagating SPR (PSPR) sensors and LSPR sensors. PSPR sensing is normally excited on continuous metal thin films through prism couplers or grating and propagating SPR can propagate along the metal surface up to hundreds of micrometers. LSPR is excited on nanostructured metal surfaces and can be adjusted by the size, shape, and composition of nanoparticles.

LSPR sensors are superior to PSPR sensors in terms of spectral tunability, but PSPR sensors exhibit better sensitivity (Zeng et al. 2014).

Nanomaterial-based enhanced SPR sensing may be based on three strategies: (a) coupling of LSPR of gold nanoparticles or silver nanoparticles with the surface plasmon wave excited on the sensing film; (b) large surface mass loading which augments the sensitivity of the SPR-sensing, for example liposomes and magnetic nanoparticles; and (c) charge transfer from the nanomaterial surface to the metallic sensing film surface, for example graphene and carbon nanotubes (Zeng et al. 2014).

The LSPR peaks of gold nanoparticles are majorly influenced by the size, shape, and dielectric constant of the neighboring medium. Controlled manipulation of the aspect ratio of gold nanorods can help to systematically tune their LSPR from the visible to the NIR region. Gold nanoparticles also offer surface chemistry to conjugate different types of analytes on the surface for enhanced specific binding to the substrate (Zeng et al. 2014). Gold nanoparticles are ideal for SPR scattering because they can resonantly scatter visible and NIR light attributed to their surface plasmon oscillation. Conjugated gold nanoparticles aggregate and have been found to induce augmented SPR scattering than their unconjugated counterparts (Chen et al. 2018). The key considerations in the development of gold nanoparticle-amplified SPR sensing include details about the target analytes such as molecular structure, concentration, and molecular weight; type of detection matrix that is water, buffer, or human serum; chemical functionalization schemes for altering the sensing film and the gold nanoparticle surface: whether thiol or amino groups; and the sensing strategy used in the study whether competitive inhibition or sandwich (Zeng et al. 2014).

Magnetic nanoparticles and carbon nanotubes have also emerged as promising SPR nanosensors and can be produced cheaply. Magnetic nanoparticles offer the advantage of enabling selective separation and detection of the desired analyte in high-viscosity samples like blood (Zeng et al. 2014). Gold nanocomposites containing gold nanoparticles in combination with magnetic nanoparticles, metallic nanoparticles, and semiconductor nanoparticles have also been explored for superior SPR sensing (Zeng et al. 2014).

SERS-based Nanosensors

In 1928, C.V. Raman discovered that when light was passed through a transparent medium, incident light and scattered light had different frequencies. This phenomenon was called 'Raman scattering'. During the passage of light through the medium, the molecules of the medium absorb incident light photons. In the majority of the cases, the molecules

re-emit photons without an exchange of energy. This is called Rayleigh scattering. However, some parts of the re-emitted photons were presented as being higher or lower than the incident photons with respect to energy, accompanied by a change in the frequency and direction. This was called Raman scattering. Both Raman and Rayleigh scattering reduced the intensity to 10^{-6} and 10^{-3} orders of magnitude respectively as compared to the intensity of incident light. Hence, the need was felt to amplify the intensity of the Raman signal (Gao et al. 2023).

Raman spectroscopy detects inelastic light scattering associated with the molecule's vibrational energy levels, resulting in the Raman fingerprint specific to the molecule. The main advantage of the Raman signal is that it permits specific detection of individual components from a complex matrix. However, conventional Raman scattering suffers from low sensitivity. The SERS technique involves the enhanced scattering of molecules positioned on and near the plasmonic surface by an enhancement factor of 10^4–10^8 (Wu D et al. 2019). SERS involves the excitation of LSPRs on the surface of nanostructured metals with incident light, thereby causing amplification of Raman scattering from molecules present near the metallic surface. It is an ultra-sensitive analytical tool endowed with inherent structural selectivity and experimental flexibility of Raman spectroscopy (Guerrini and Alvarez-Puebla 2019).

The SERS phenomenon was initially observed by Fleischmann in 1974 when studying pyridine adsorbed on a roughened silver electrode. The enhanced Raman signal can be attributed to electromagnetic and chemical enhancement mechanisms. In electromagnetic enhancement, when a molecule is in the proximity of a plasmonic nanostructure, it experiences an enhanced field called local field enhancement. The molecule then radiates with augmented efficiency. Chemical enhancement involves charge transfer between the nanoparticles and the analyte (Beeram et al. 2023). Chemical enhancement requires that the distance for electron transfer between the modified molecules and the nanoparticles must be less than 10 nm (Gao et al. 2023). Electromagnetic enhancement is the major mechanism (enhancement contribution of 10^4–10^7) and chemical enhancement is the minor contributor (enhancement contribution of 10–10^2) (Kahraman et al. 2017).

The SERS efficiency is governed by the type of plasmonic material, selection of wavelength, surface coverage of the molecules, and analyte concentration (Beeram et al. 2023). When the wavelength of the surface plasmons of the nanostructure is situated between the excitation wavelength and the wavelength of the Raman signal, higher SERS enhancement is observed (Kahraman et al. 2017). Noble materials such as copper, gold and silver and their alloys are commonly utilized for SERS because of their inertness, tunability in the visible and NIR regions, sensitivity, and compatibility (Beeram et al. 2023). When colloidal noble

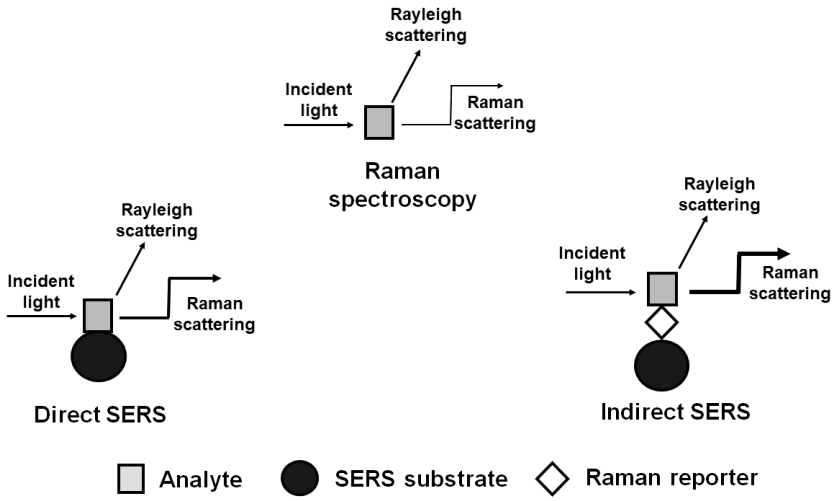

Fig. 2. Schematic representation of direct and indirect SERS. ⏎

metal nanoparticles are used, one must consider the surface charge of the nanoparticles and the charge of the molecules. The opposite charge of detecting molecules with respect to the surface charge of nanoparticles results in stronger SERS activity (Kahraman et al. 2017). However, the usage of noble metals is associated with the risk of oxidation, poor stability, agglomeration, and high cost. The usage of semiconductor nanomaterials is an alternative as they possess better chemical stability and can be fabricated in a controlled manner. However, their SERS sensitivity is lower than that of noble metals (Lin et al. 2023).

SERS-based measurements can be conducted in direct and indirect ways (Fig. 2).

The direct approach involves loading the analyte onto the surface of the SERS substrate and measuring its Raman spectrum without using any Raman label. However, in this approach, the intensity of the Raman signal could be better due to poor adsorption of the analyte coupled with low polarization and the weak Raman scattering characteristics of the analyte (Gholami et al. 2020). Urine analysis of a patient to diagnose and monitor relapse of prostate cancer, detection of ulcerative colitis in plasma, characterization of hepatitis C viral ribonucleic acid (RNA) extracted from various blood samples of Hepatitis C virus patients, and monitoring the efficacy of anti-platelet therapy are few examples where label-free SERS analysis has been explored (Szaniawska and Kudelski 2021). The indirect approach involves the detection of the target molecule via its interaction with a Raman reporter, which has a strong Raman scattering ability. The reporter molecule is loaded with the SERS substrate, and the Raman spectrum is recorded. When the analyte is brought in contact with the SERS

substrate, the intensity of the Raman signal changes, thereby enabling the detection of the analyte. The indirect approach is reproducible and enables analyte detection with a low limit of detection (LOD) (Gholami et al. 2020). 4-Mercaptopyridine (MPy) and 4-mercaptobenzoic acid are two pH-sensing molecules commonly utilized in SERS-based detection endowed with an excellent affinity for the surface of gold nanoparticles (Jahn et al. 2020).

SERS offers high selectivity and decreases photobleaching (Bozal-Palabiyik et al. 2019). SERS is a promising technique for selective, sensitive, and accurate detection of subtle changes in intracellular parameters such as pH, redox potential, and reactive oxygen species (ROS), which are indicative of specific biological and pathological processes (Wu D et al. 2019). SERS is also employed for liquid biopsy of tumors to facilitate rapid and non-invasive estimation of cancer biomarkers such as circulating tumor cells in body fluids (Guerrini and Alvarez-Puebla 2019). SERS is compatible with liquid samples rendering it suitable for liquid biopsy (Beeram et al. 2023). The SERS technique has gained popularity in healthcare due to its simplicity, non-destructive detection, and advances in plasmonics and instrumentation. The SERS technique has been widely utilized for disease detection in an array of biological matrices including blood, plasma, breath, saliva, urine, tears, etc. (Beeram et al. 2023). The SERS technique requires a very small quantity of sample (picoliters) (Kahraman et al. 2017). An important challenge in using SERS for analyte detection is the background interference from the analyte environment. Impurities present in the physiological milieu compromise the sensitivity of SERS (Lin et al. 2023).

Photoacoustic Imaging-based Nanosensors

Photoacoustic imaging involves the absorption of photons by a molecule and transformation to ultrasound waves through the photoacoustic effect (Fig. 3).

Photoacoustic imaging provides imaging depths up to several cm with acoustically defined spatial resolution which is not possible with fluorescence imaging (Cash et al. 2015).

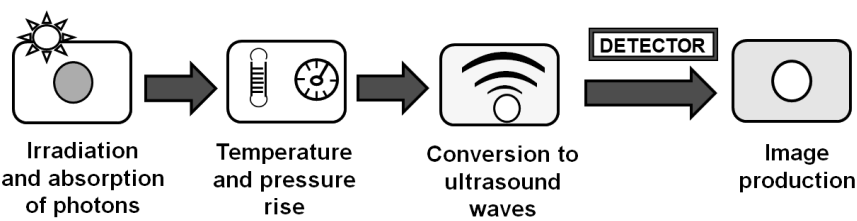

Fig. 3. Schematic diagram of photoacoustic imaging.

The photoacoustic effect was discovered by Bell in 1880. Irradiation of tissue by light results in the penetration of photons into the tissue up to a certain depth. Photons are scattered and absorbed by the molecules of the chromophore. The absorbed energy is transformed into heat by vibrational and collisional relaxation. This results in raised pressure and subsequent emission of acoustic waves. The pressure wave termed the photoacoustic signal then propagates to the surface for its detection (Jin et al. 2022). Most excitation sources utilized in photoacoustic imaging are between 680 nm and 1100 nm since NIR light has superior penetration depth than optical light because of lower hemoglobin absorption and tissue scattering (Lemaster and Jokerst 2017).

Photoacoustic imaging technique unites the advantage of the depth of imaging associated with ultrasound and superior image contrast offered by optical imaging. The technique is non-invasive and biocompatible (Rong et al. 2019). Photoacoustic imaging is more sensitive, economical, and faster compared to magnetic resonance imaging (MRI) and computed tomography (CT) (Karthikesh and Yang 2020). Photoacoustic imaging is a safer option than positron emission tomography and CT which utilize ionizing radiation. It also provides high imaging contrast between diseased and healthy tissues. The photoacoustic effect provides real-time information on the cellular and molecular signatures of the biological tissues. Probes for photoacoustic imaging may be based on nanoparticles or organic dyes. Gold nanoparticles, gold nanorods, palladium nanosheets, copper sulfide nanoparticles, carbon and its combined metallic nanomaterials, and semiconducting polymer nanoparticles have been explored as contrast agents for photoacoustic imaging (He et al. 2022).

The photoacoustic effect has been widely used to detect blood glucose, blood oxygen, and cancer cells; and for atherosclerosis imaging (Jin et al. 2022). Photoacoustic imaging has demonstrated its prowess in guiding surgeries (visualization and differentiation of structures during surgeries), biopsies (vision-based robot control of biopsy needle tips passage in obese patients), drug delivery (monitoring drug release from the formulation), and therapies (ultrasound therapy, laser ablation, targeted antibacterial therapy, and stem cell therapy) non-invasively in real-time (Karthikesh and Yang 2020).

Photoacoustic imaging has been combined with Raman spectroscopy in ovarian cancer. Photoacoustics differentiated between tumor and normal tissue, whereas Raman spectroscopy guided surgical resection (Jokerst et al. 2012). Triple modality nanoparticles combining MRI, photoacoustic imaging, and Raman spectroscopy have been used for glioma resection (Kircher et al. 2012).

However, the instrumentation for photoacoustic imaging is complex as compared to fluorescence imaging (Cash et al. 2015). Further, interference

from environmental factors is another challenge in photoacoustic detection (Jin et al. 2022). Reducing artifacts during the reconstruction of the photoacoustic image from the signals requires complicated algorithms and a long processing time (Karthikesh and Yang 2020). Reproducibility and standardization of photoacoustic images pose a challenge to the standard-of-care medical use of photoacoustic imaging (Steinberg et al. 2019).

Advances in Optical Nanosensors

Optical Nanosensors based on in situ Formation of Nanomaterials

Optical nanosensors based on the *in situ* formation of nanomaterials are a recent breakthrough preferred owing to their ease of operation and cost. In the case of these nanosensors, analytes are responsible for triggering the growth of nanomaterials in the detection system leading to color change or fluorescence change in the detection system, facilitating the detection of analytes. This kind of system eradicates the arduous preparation and purification procedures since detecting analytes and forming nanomaterials occur concurrently. In these systems, the starting materials for assembling nanomaterials and analytes are blended in aqueous solutions. Colorimetric nanosensors are usually based on *in situ* generation of gold and silver nanoparticles. Few analytes can cause reductive transformation of $AuCl_4^-$ or Ag^+ ions into gold or silver nanoparticles, causing color changes due to the SPR effect. Fluorimetric nanosensors based on *in situ* formation involve *in situ* fabricated cadmium sulfide quantum dots, fluorescent silver nanoparticles, fluorescent silicon nanoparticles, and fluorescent copper nanoparticles. There are a few challenges associated with *in situ* colorimetric and fluorescent nanosensors. Firstly, currently existing colorimetric *in situ* nanosensors are based on gold and silver nanoparticles. There is a need to develop materials that have low cost and toxicity. Further, the majority of the detection mechanisms are based on signal off which is easily influenced by the detection environment causing inaccurate detection. Ratiometric testing would be beneficial to avoid the influence of the detection medium and enhance the accuracy of detection. Also, developing point-of-care diagnostic platforms based on *in-situ* formation of nanomaterials is essential. Lastly, these nanosensors based on *in-situ* generation of nanomaterials need to be upgraded further to possess better sensitivity, selectivity, and response time (Guo and Zhao 2019).

Multimodal Diagnosis using Optical Nanosensors

A single imaging modality may sometimes be inefficient due to poor tissue penetration depth, low contrast, low sensitivity, and compromised spatial resolution. Hence, a combination of imaging modalities is used to complement the features of both imaging techniques (Li et al. 2017). Examples of multimodal diagnosis include dual colorimetry and fluorimetry, fluorescence and SERS, and fluorescent imaging and photoacoustic imaging.

Colorimetric analysis is simple, economical, and enables visual detection. Fluorimetric analysis is selective and sensitive. Dual colorimetric-fluorimetric analysis combines the benefits of both techniques (Hallaj et al. 2021). Research works exploring dual colorimetric-fluorimetric analysis have been discussed in the sub-sections 'Diagnosis of renal dysfunction' and 'Therapeutic drug monitoring and therapeutic efficacy monitoring'. Fluorescent-SERS nanosensors combine the advantage of high specificity of fluorescent probes with the ability of Raman scattering to avoid photobleaching. Li and group synthesized a compound MDPA containing a mercaptoacetic acid (MPA) and a di-(2-picolyl) ethylenediamine moiety 16 (DPA). MDPA was then covalently bound onto gold nanoparticles via Au-S linkage. MDPA shows good chelating capacity with Zn^{+2}, large Raman cross-section, and good binding with gold nanoparticles. On exposure to different concentrations of Zn^{+2}, aggregation of MDPA gold nanoparticles occurs due to coordinate bond formation between N of MDPA and Zn^{+2}, generating a fluorescent and SERS response. The developed nanosensor was biocompatible and enabled intracellular imaging and quantification of Zn^{+2} (Li et al. 2018). Few more research works exploring dual fluorescent-SERS analysis have been discussed in the sub-sections 'Detection of pH' and 'Detection of oxidative stress'. NIR fluorescent (NIRF) and photoacoustic imaging may be combined for real-time imaging in cancer (Li et al. 2017). Research works exploring dual fluorescent and photoacoustic imaging in cancer have been discussed in the sub-section on theranostics.

Applications of Optical Nanosensors in Healthcare

Optical nanosensors have a myriad of applications in healthcare including diagnosis of diseases, detection of molecules or phenomena indicative of disease, drug assays in pharmaceutical dosage forms, detection of drug abuse, therapeutic drug monitoring and therapeutic efficacy monitoring, and theranostics as given below.

Diagnosis of Diseases

Optical nanosensors have been explored for the diagnosis of diseases including cancer, neurodegenerative disorders, infections, diabetes, cardiovascular diseases, and renal dysfunction as given below.

Cancer

Widely used cancer screening tools include mammography, occult blood detection, CT scan, MRI, ultrasound imaging, etc. However, these tools are expensive and cannot detect cancer in its early stages (Nosheen et al. 2019). Optical nanosensors have been developed to detect various biomarkers associated with cancer as given below.

Vascular endothelial growth factor-165 ($VEGF_{165}$) is an important biomarker in cancer angiogenesis. Zhu et al. developed fluorescent Mn-doped ZnS quantum dots to detect $VEGF_{165}$. Aptamer, modified with biotin at the 3′ end, Mn-doped ZnS quantum dots at the 5′ end, and black hole quencher-2 (BHQ-2) quencher labeling strands were linked to streptavidin-functionalized silver nanoparticles. The addition of BHQ-2 quenches the fluorescence of the quantum dots due to FRET. However, when the nanosensor is exposed to $VEGF_{165}$, the BHQ-2 strands are displaced, interrupting FRET and restoring the fluorescent signal. Due to the incorporation of silver nanoparticles, the metal-enhanced fluorescent effect is seen, which further increases the sensitivity of the nanosensor compared to a plain fluorescent nanosensor based on Mn-doped ZnS quantum dots (Zhu et al. 2015).

Hosu et al. developed a colorimetric immunosensor coupled with a smartphone to detect cancer antigen 125 (CA125). The primary antibody was immobilized by spotting onto the 3D nitrocellulose membrane. The immunospots were then incubated with CA125 solution followed by affinity-based interaction with secondary antibody-conjugated polyethylene glycol (PEG)ylated gold nanoparticles. The antibody-conjugated gold nanoparticles were captured onto the immunospots, causing silver deposition from a silver enhancer solution to form gold-silver nanoparticles of various grey color spots related to CA125 concentration. Also, an 8-megapixel smartphone camera was included in a homemade dark box to serve as the transducer of color image acquisition and data handling. The developed nanosensor showed good sensitivity with a LOD of 30 U/ml and selectivity for CA125 estimation without interference from VEGF (Hosu et al. 2017).

Human epididymis protein 4 (HE4) and CA125 are biomarkers for ovarian cancer approved by the US FDA. However, the levels of these biomarkers in serum are deficient during the early stages of ovarian cancer, thus precluding early detection of the disease. There is an unmet need

for an implantable nanosensor implanted in or near the ovary, fallopian tube, or uterine cavity. Williams et al. designed a carbon nanotube-based sensor for the optical detection of ovarian cancer biomarker HE4 *in vivo*. They designed antibody-functionalized carbon nanotubes that can quantify HE4 levels through modification of nanotube optical bandgap. Implantation of the nanosensor in the peritoneal region in murine ovarian cancer models showed the ability of the nanosensor to detect HE4 levels and differentiate between HE4-producing and non-HE4-producing tumors. The nanosensors exhibited a blue shift in HE4-expressing ovarian tumors and no shift or red shift in HE4 non-producing tumors (Williams et al. 2018).

Prostate-specific antigen (PSA) is an excellent biomarker for preoperative detection and screening of prostate cancer and postoperative monitoring. PSA is a serine protease that cleaves the peptide bond via hydrolysis. Xia et al. designed a gold-coated magnetic microbead-based nanosensor for the colorimetric detection of PSA. Ascorbic acid acts as a reducing agent for making gold nanoparticles from $HAuCl_4$. Cu^{2+} ion is reported to facilitate the oxidation of ascorbic acid, thereby preventing the formation of gold nanoparticles. Immobilization of a peptide cleavable by PSA onto the surface of gold-coated magnetic microbeads sequesters the Cu^{2+} ion. It inhibits the Cu^{2+}-catalysed oxidation of ascorbic acid, thereby promoting the formation of gold nanoparticles. The presence of PSA cleaves the peptide sequence, thereby hindering the formation of gold nanoparticles. The method was linear in the 0–0.8 ng/mL range with a LOD of 0.02 ng/mL. The developed method lacked interference from components in the biological matrix due to the distinction between the cleavage step and measurement steps (Xia et al. 2018).

A drawback of fluorescence-based immunoassays is that they utilize antibodies as recognition elements associated with escalated costs and issues of denaturation and deactivation. Oligopeptides are more beneficial than antibodies regarding stability in harsh environments and cost. Yang et al. developed a peptide/magnetic nanocomposite-based fluorescent nanosensor for selective and sensitive detection of PSA via self-assembly of FAM-peptide onto the surface of magnetic nanocomposites. FAM-peptide (specific oligopeptide labeled by 5-FAM) was employed as a fluorescence-emitting element and molecular recognition element. The magnetic nanocomposites produced via *in situ* deposition of gold nanoparticles around silicon dioxide encapsulated Fe_3O_4 nanocubes helped to quench the fluorescence of FAM-peptide and enabled easy magnetic separation in the solution to reduce background interference. When the nanosensors encounter PSA, PSA specifically recognizes and cleaves the FAM-labelled peptides, causing fluorescence recovery (Yang et al. 2018).

Shayesteh and Gavami developed a colorimetric method for quantifying PSAs in serum using aptamer-conjugated gold nanoparticles.

They employed water-soluble cationic polymer poly(diallyldimethylamm oniumchloride) (PDDA) to control the aggregation of gold nanoparticles. Initial capping of the gold nanoparticles with negatively charged citrate protects the former against aggregation, and the SPR peak is seen at 520 nm. However, on addition to positively charged PDDA, PDDA interacts with negatively charged citrate via electrostatic bonding, causing aggregation of gold nanoparticles and a new peak at 680 nm. Conjugation of Poly A aptamer to gold nanoparticles causes the formation of polyA aptamer-PDDA complex (formed via electrostatic interactions between negatively charged phosphate of aptamer and positively charged PDDA), and gold nanoparticles get stabilized due to citrate showing red color. When PSA comes in contact with the nanosensor, Poly A aptamer binds to it, thereby causing the release of PDDA, which then induces aggregation of gold nanoparticles changing color to purple. The ratio of the absorbance of the peak produced by gold nanoparticles in the aggregated state to the peak produced in the dispersed state ($A_{680/520}$) is utilized to quantify PSA in the sample. The developed nanosensor offers a simple, cost-effective, selective, and sensitive probe for early diagnosis of prostate cancer (Shayesteh and Ghavami 2020).

Cancer cells majorly depend on glucose and glutamine for intermediary metabolism. Hence, the measurement of intracellular glucose levels serves to indicate cancer proliferation. Quantum dots are ideal probes for long-term monitoring of intracellular environments due to their exclusive optical characteristics. They show long photoluminescence decay times, more than the lifetime of the cell's autofluorescence, which facilitates the distinction of the signal of quantum dots from the intracellular background signal. Further, the photoluminescence lifetime of quantum dots is extremely sensitive to environmental variations. Ripoll et al. fabricated quantum dot-based conjugates as sensors for monitoring intracellular glucose levels in live cells using Fluorescence Lifetime Imaging Microscopy (FLIM). Aminophenylboronicacid was tethered onto the surface of CdSe/ZnS quantum dots quenching the photoluminescence of the latter. When the nanosensor encounters glucose inside the cells, photoluminescence is recovered, and fluorescence lifetime enhancement permits quantifying intracellular glucose levels. The nanoparticles were found to internalize into MDA-MB-231 cancer cells via endocytosis and could detect intracellular glucose level variations when combined with FLIM (Ripoll et al. 2019).

Apurinic/apyrimidinic endonuclease 1 (APE1) is overexpressed in many cancer cells, including breast, ovarian, colorectal, liver, prostate, lung, pancreatic, cervical, and leukemia. Thus, APE1 is a potential biomarker for cancer diagnosis, cancer prognosis, monitoring cancer therapy, and checking for cancer relapse. Zhang et al. developed nanocomposites containing graphene quantum dots and unimolecular DNA, in which

DNA molecules were tethered onto the graphene quantum dots via adsorption. Unimolecular DNA structures contain four components: (a) an AP site-containing double-stranded structural unit, which is cellular APE1's substrate; (b) a single-stranded DNA segment to facilitate adherence of DNA structural entity onto surfaces of graphene quantum dots; (c) a fluorophore (Cy3) covalently bound to APE1's substrate, the signals of which are quenched by graphene quantum dots before action of cellular APE1 and resurface on catalytic activity of cellular APE1; and (d) a short single-stranded hairpin loop for stabilizing the duplex unit of APE1 substrate. Graphene quantum dots play the dual role of quenching the fluorescence of Cy3 in APE1 substrates before the catalytic action of cellular APE1 and permit cytoplasmic ingress of the nanocomposites through endocytosis (Zhang H et al. 2020).

Liu et al. developed a SERS-based paper nanosensor for the non-invasive, sensitive, and rapid detection of oral cancer. Exfoliative cells from the person's mouth can be collected on the plasmonic paper nanosensor and SERS can be used to detect cancer. Exfoliated cells from normal and cancer tissues generate different spectra in SERS, which is attributed to structural and metabolic changes. Exfoliated cells from the normal tissue produce lipid-dominated spectra whereas those from the cancerous tissue produce protein-dominated and DNA-dominated spectra. Gold nanorods were employed as plasmonic nanostructures because of their strong SPR extinction in the NIR region, good stability, and minimal toxicity. The paper-based nanosensor is cost-effective, storable, bio-degradable, and can be easily fabricated (Liu et al. 2014).

Neurodegenerative Disorders

Recent times have witnessed a surge in neurodegenerative disorders with a rise in the average lifespan. There is an urgent need to develop diagnostic tools for early and precise detection of neurodegenerative disorders like Alzheimer's disease and Parkinson's disease (Karaboğa and Sezgintürk 2022).

Liu and group synthesized nanosensors based on CDs-sensitized lanthanide infinite coordination polymer (ICP) nanoparticles for detecting beta-amyloid (Aβ) monomer, a biomarker of Alzheimer's disease. They first synthesized CDs with many amino and carboxyl groups. These CDs were an antenna ligand to promote the self-assembly of Eu^{3+} and 5′-guanosine monophosphate disodium (GMP) to form CDs@Eu/GMP ICP nanoparticles. The CDs@Eu/GMP ICP nanoparticles showed the characteristic emission of CDs at 400 nm and the characteristic emission of Eu^{3+} at 592 nm, 615 nm, 650 nm, and 694 nm. When there is Cu^{2+}, the coordination interaction between CDs and Cu^{2+} disturbs the antenna effect causing quenching of the fluorescence of Eu^{3+}. However, the fluorescence

of CDs at 400 nm does not change as an internal reference to achieve a built-in correction for ratiometric fluorescent sensing of Aβ monomer. In the presence of the Aβ monomer, the stronger coordination between the Aβ monomer and Cu^2 restored the fluorescence of Eu^{3+}. The method was sensitive and selective in detecting Aβ monomer in rat brain (Liu et al. 2020).

Dopamine is a crucial neurotransmitter whose deficiency is seen in diseases like Parkinson's disease, restless legs syndrome, and attention deficit hyperactivity disorder. Detection of dopamine in the presence of ascorbic acid is a challenge since ascorbic acid interferes with the estimation of dopamine (Ankireddy and Kim 2015). Ankireddy and Kim developed water-soluble indium phosphide/zinc sulfide quantum dots functionalized with L-cysteine to enhance selectivity for dopamine. When the quantum dots were exposed to increasing dopamine levels, they showed fluorescence quenching. The developed nanosensor showed a LOD of 875 pM and could detect dopamine in the presence of ascorbic acid (Ankireddy and Kim 2015).

Diaz-Destra and group designed ZnS:Mn quantum dots functionalized with cysteine to detect dopamine in biological matrices containing several interfering substances. Dopamine gets oxidized to dopamine quinone at alkaline pH and gets absorbed onto the ZnS:Mn quantum dots via hydrogen bonding and electrostatic linkage with the L-cysteine modification on the surface of quantum dots. The oxidized quinone acts as an electron acceptor and quenches the phosphorescence of quantum dots. The nanosensor successfully estimated dopamine levels in urine in the presence of interfering substances such as glucose and chloride ions. The developed nanosensor was based on the phenomenon of phosphorescence, which is beneficial since biological fluids do not exhibit substantial phosphorescence, thus increasing the signal-to-noise ratio for the sensor (Diaz-Diestra et al. 2017).

Ban et al. designed mono-6-amino-β-cyclodextrin (NH_2-β-CD)-functionalized gold nanoclusters to detect dopamine. When the nanosensor was exposed to dopamine, dopamine interacted with the β-cyclodextrin cavity on the surface of gold nanoclusters, thus causing the oxidation of dopamine to quinone form, thereby quenching the fluorescence of gold nanoclusters. The developed nanosensor showed excellent sensitivity with a LOD of 2 nM and successfully estimated dopamine without any interference from ascorbic acid and uric acid (Ban et al. 2015).

Wen et al. developed β-cyclodextrin-decorated gold nanoparticles for colorimetric detection of dopamine. The developed nanosensor showed a LOD of 20×10^{-9} M. When the nanosensor is exposed to dopamine; the gold nanoparticles undergo assembly and color changes. Dopamine-induced assembly of gold nanoparticles could be attributed to the host-guest interaction between β-cyclodextrin and dopamine and the interaction

between dopamine and gold nanoparticles. The nanosensor showed good selectivity for dopamine with no interference from glucose, uric acid, and ascorbic acid. It successfully estimated dopamine levels in artificial cerebrospinal fluid and human blood serum (Wen et al. 2016).

Infections

Infectious diseases are a grave health concern claiming millions of lives, especially in developing nations. Conventional methods used for the diagnosis of infections such as culturing, microscopy, Enzyme-linked Immunosorbent Assay (ELISA), and Polymerase Chain Reaction (PCR) have their disadvantages. Culturing is time-consuming and microscopy is limited by the small size of pathogens. PCR and ELISA are sophisticated techniques requiring trained personnel and expensive equipment. Simple, quick, and economical sensing strategies for accurate diagnosis of infections are the need of the hour in resource-limited settings (Deng et al. 2021). Optical nanosensors have been explored for the detection of bacterial, fungal, and viral infections as given below.

Inner filter effect (IFE) refers to a phenomenon responsible for fluorescence quenching, wherein absorption bands of the absorber overlap with excitation or emission bands of the fluorophores. IFE does not need covalent interaction between the fluorophore and quencher (Ding et al. 2018).

Adib et al. developed an ingestible nanosensor for the detection of *Helicobacter pylori* infection. They immobilized UCNPs ($NaYF_4$:Yb, Er, Lu@ PEG-NH_2), red cabbage-extracted anthocyanins, and iron oxide (Fe_3O_4) nanoparticles within the 3-dimensional scaffold of chitin nanofiber paper. They combined this with smartphone technology for smart diagnosis. The sensing strategy was based on the *Helicobacter pylori* urease-mediated conversion of urea to liberate ammonia. This change in pH changes the pH-dependent fluorescence/color profile of the developed sensor through IFE. Iron oxide nanoparticles aid in precisely controlling the location of the ingestible sensor in the stomach through an external magnetic field. The optically transparent nature of chitin nanofiber paper helps in *in-vivo* monitoring (Adib et al. 2023).

Point-of-care systems for ultrasensitive detection of tetanus antibodies in serum are imperative to reduce the risk of tetanus infection. Chen et al. fabricated fluorescent nanospheres and incorporated them in a portable lateral flow test strip to estimate tetanus antibodies in human serum. Goat anti-human IgG (Fc) was coupled onto the surface of fluorescent nanospheres. The test strip contained a test line loaded with tetanus antigen and a control line loaded with goat anti-human IgG. When the sample containing tetanus antibody is loaded onto the strip, it migrates along the strip owing to the capillary effect. The fluorescent nanosphere-

antibody (Fc)/tetanus antibody complexes are captured onto the test line via interaction between the tetanus antigen and the antibody. The remaining antibody (Fc)-fluorescent nanosphere complex is captured by goat anti-human IgG on the control line. When the sample does not contain a tetanus antibody, the antibody (Fc)-fluorescent nanosphere conjugate only binds to the goat anti-human IgG on the control line, and the test gives a negative result. The test and control lines' fluorescent signals are recorded to quantify the tetanus antibody present in the sample. The nanospheres showed a 100-fold lower LOD for tetanus antibodies than gold-based lateral flow test strips. The detection could be completed within 10 min (Chen et al. 2020).

Invasive pulmonary aspergillosis is a serious fungal infection affecting the lungs. Galactomannan, a polysaccharide antigen in the cell wall of *Aspergillus* fungi is an important diagnostic marker for the disease. The currently used ELISA method is tedious, time-consuming, requires a lot of washing, and is qualitative or semi-quantitative. Alanichev et al. developed a nanosensor based on analyte-induced aggregation for the detection of *Aspergillus* galactomannan in clinical broncho-alveolar lavage (BAL). The group used gold nanoparticles functionalized with high-affinity antibodies for galactomannan. Aggregation of the nanoparticles was assessed using the hydrodynamic diameter of the conjugates and the relative intensity of the light scattered by them. The developed method was faster and simpler compared to ELISA with a good correlation with ELISA and excluded the washing step. The nanosensor showed a low LOD of 3 ng/ml by the hydrodynamic diameter detection and 0.4 ng/ml by the intensity of scattered light detection in BAL samples (Alenichev et al. 2022).

Duyen and group developed a colorimetric nanosensor for rapid detection of dengue virus. The sensing approach was based on the binding of DNA-conjugated gold nanoparticles to genomic RNA of dengue resulting in the formation of DNA-RNA heteroduplex structure which transforms the ruby red color of colloidal gold to blue because of nano-aggregation in an acidic milieu. The DNA probe was designed to bind to a genomic RNA-conserved region known in all four dengue serotypes. The developed nanosensor was able to detect dengue virus serotype 1 with excellent specificity with a LOD of 1 pg/µl in about 1 h (Duyen et al. 2023).

Lew and group developed a colorimetric serological assay to detect SARS-CoV-2 antibodies in patient plasma. They conjugated short antigenic epitopes to gold nanoparticles. Selective bivalent binding between the epitope-conjugated gold nanoparticles and the antibodies causes nanoparticle aggregation which is reflected as a unique optical transition in the gold nanoparticles' plasmon characteristics within 30 min of antibody introduction. The optimized nanosensor could identify SARS-

CoV-2 infection with 100% selectivity and 83% sensitivity in 35 clinical plasma samples of varied illness severity (Lew et al. 2021).

Diabetes

Diabetes is counted among the most common and challenging diseases of the 21st century. Regular monitoring of blood glucose levels in diabetes patients is vital (Mofidi et al. 2023). Optical nanosensors have an advantage over electrochemical nanosensors for diagnosing diabetes. Electrochemical nanosensors may suffer from interference from electroactive molecules like urea, ascorbate, etc. Optical nanosensors also provide non-invasive glucose monitoring (Gao et al. 2016).

Li et al. synthesized enzyme-mimic nanosensors based on mesoporous silica microspheres. They incorporated CdTe quantum dots in the core and gold nanoparticles in the mesoporous silica shell. Gold nanoparticles in the shell function as glucose oxidase enzyme and mimic catalyzing the glucose conversion, generating H_2O_2. This causes quenching of CdTe photoluminescence owing to charge transfer. The nanosensor showed a linear range of 5 to 200 μM and a LOD of 1.32 μM for glucose detection (Li et al. 2014).

There is a growing focus on developing non-enzymatic nanosensors to avoid the drawbacks of high cost and poor shelf life associated with enzymes. Du et al. developed amino-functionalized silicon quantum dots using an easy microemulsion technique as a non-enzymatic nanosensor to detect glucose. Silicon quantum dots suffer from poor solubility in water. Hence, allylamine modification was carried out to improve water solubility. The developed quantum dots showed good optical stability, excellent fluorescent quantum yield, and high water-solubility. Exposure of the developed nanosensor to increasing concentrations of glucose resulted in the quenching of fluorescence of the quantum dots. Glucose molecules were found to link the quantum dots through hydrophobic interactions and hydrogen bonding causing self-aggregation of the quantum dots, thereby quenching their fluorescence. The nanosensor demonstrated linearity in the 1×10^{-6} to 9×10^{-5} moles/liter and LOD of 3×10^{-7} moles/liter for glucose (Du et al. 2019).

Duan et al. developed tungsten disulfide (WS_2) quantum dots to detect glucose based on the conversion of Fe^{2+} to Fe^{3+} and enzymatic reaction. Fe^{3+} quenches the fluorescence of WS_2 quantum dots via photoinduced electron transfer, whereas Fe^{2+} does not induce quenching. The glucose oxidase enzyme converts glucose to gluconic acid and H_2O_2. H_2O_2 causes the conversion of Fe^{2+} to Fe^{3+}, thereby quenching the fluorescence of WS_2 quantum dots. The nanosensor showed a LOD of 0.3 μmoles/liter and was successfully employed for glucose estimation in serum samples (Duan et al. 2019).

Vaishanav et al. loaded Mn^{2+}-doped CdTe/ZnS quantum dots immobilized with glucose oxidase enzyme on a bioactive cellulose paper strip for quick and sensitive visual estimation of glucose in human blood and urine. The quantum dots were functionalized with glutathione for conjugating glucose oxidase onto them. The fluorescence signal of Mn^{2+}-doped CdTe/ZnS quantum dots is sensitive to H_2O_2 levels and decreases with increased H_2O_2 levels. Oxidation of glucose by the enzyme glucose oxidase produces H_2O_2. Doping of the quantum dots with Mn^{2+} enhanced the nanosensor's sensitivity. The developed paper strip nanosensor was dipped into the sample, and the resulting color change was monitored in UV light to estimate glucose. The developed nanosensor thus provided an economical and sensitive point-of-care diagnostic module for detecting glucose in blood and urine (Vaishanav et al. 2017).

Gao et al. designed poly-L-lysine coated nanosensors (150 nm) containing a reference dye coumarin six, an oxygen probe in the core, and glucose oxidase in the outer shell. Glucose oxidase molecules on the surface of the nanosensor catalyze the conversion of glucose consuming oxygen which is detected by the oxygen probe present in the core of the nanosensor. The developed nanosensors had a short response time of 2 to 4 min (Gao et al. 2016).

Wu et al. developed bifunctional nanosensors for ratiometric fluorescent detection of hydrogen peroxide and glucose. They designed glutathione-functionalized gold nanoclusters to mimic the peroxidase enzyme's action and cause hydrogen peroxide's conversion to form OH. radicals. This radical causes the oxidation of terephthalic acid, which is non-fluorescent, to form hydroxyterephthalate, which is fluorescent. The glutathione-modified gold nanoclusters show emission at 600 nm on excitation, and hydroxy terephthalate shows emission at 430 nm. The fluorescent emission signal of hydroxy terephthalate increases with an increase in hydrogen peroxide concentration; however, the fluorescence of glutathione-modified gold nanoclusters remains unchanged. The developed nanosensor was also successfully used to detect glucose concentrations in human serum samples by using glucose oxidase enzyme, which converts glucose to gluconic acid and hydrogen peroxide (Wu Y et al. 2019).

Cardiovascular Diseases

Cardiovascular diseases are the major cause of death globally (Nazir and Iqbal, 2023). Conventional methods of molecular imaging used to diagnose cardiovascular disease including CT, MRI, and electrocardiogram suffer from poor sensitivity and selectivity (Shi et al. 2020). Detection of cardiac biomarkers at the early stages of heart disease is essential to decrease the mortality rate (John et al. 2022). Optical nanosensors have been explored

for the detection of biomarkers associated with cardiovascular disease as given below.

Increased blood levels of cholesterol escalate the risk of hypertension, atherosclerosis, and coronary heart diseases. Li et al. fabricated a nanosensor based on the combination of FRET and competitive host-guest recognition for detecting cholesterol. They synthesized β-cyclodextrin@ gold nanoparticles using chloroauric acid as a precursor and β-cyclodextrin as a reducing agent. Positively charged carbon quantum dots were also utilized in the nanosensor design via host-guest interactions between β-cyclodextrin and carbon quantum dots. Carbon quantum dots and β-cyclodextrin@gold nanoparticles demonstrated the FRET phenomenon wherein carbon quantum dots and β-cyclodextrin@gold nanoparticles acted as fluorescence energy donor and fluorescence energy acceptor, respectively, resulting in quenching of fluorescence of carbon quantum dots. When the nanosensor comes in contact with cholesterol, cholesterol replaces carbon quantum dots from the cavity of β-cyclodextrin@ gold nanoparticles, thus causing recovery of fluorescence of the carbon quantum dots. The developed nanosensor demonstrated linearity in the 10 to 210 μmoles/L range and showed a LOD of 343.48 nmoles/L for cholesterol (Li et al. 2019).

C-reactive protein is recognized as a clinical biomarker for the prediction of the risk of cardiovascular disease. Antonio et al. developed a colorimetric nanosensor for detecting C-reactive protein using citrate-capped gold nanoparticles and a C-reactive protein binding aptamer. The aptamer was adsorbed onto the surface of gold nanoparticles, thus preventing their aggregation. However, when the nanosensor was exposed to C-reactive protein in the presence of salt, the aptamer bound to it caused aggregation of gold nanoparticles resulting in a color change from red to purple. C-reactive protein levels in the sample could be quantified from the absorbance ratio at 670 nm to that at 520 nm (A_{670}/ A_{520}). The sensor permitted quick estimation of C-reactive protein without interference from bovine serum albumin (António et al. 2020).

Park et al. developed a fluorescent nanosensor for imaging ROS-producing pro-inflammatory macrophages in atherosclerotic plaques. Hyaluronic acid as a ligand for the CD44 receptor and chlorin e6 (Ce6) as a NIRF dye were conjugated via a thioketal linker. The developed self-assembled nanosensor produced feeble signals in a typical physiological environment owing to fluorescence quenching of Ce6 by the proximal distance between Ce6 molecules within the nanosensor. On systemic administration, the nanosensor selectively bound to CD44 on macrophages in the plaques and was internalized into pro-inflammatory macrophages via the CD44 receptor. Intracellular ROS in pro-inflammatory macrophages induced cleavage of thioketal linkage, causing prominent recovery of NIRF signal. Confocal microscopy and immunohistological analyses

confirmed the capacity of the developed nanosensor to image CD44 and ROS-overproducing pro-inflammatory macrophages in atherosclerotic plaques (Park et al. 2020).

Renal Dysfunction

The human kidney is a significant excretory organ responsible for filtering out metabolic wastes. Nanosensors may be utilized to detect chronic kidney disease at an early stage via urinary analysis, breath analysis, and contrast imaging (Yang et al. 2023).

Human serum albumin is a plasma protein found in the human body. However, its presence in urine indicates a hepatic or renal dysfunction. Esenturk et al. designed a SPR-based gold nanosensor chip coated with human serum albumin-imprinted nanoparticles to detect microalbumin in urine. The nanoparticles comprised ethylene glycol dimethacrylate as a cross-linker and N-methacryloyl-L-leucine as a monomer. The nanosensor exhibited a LOD of 0.7 pM and a limit of quantification of 1.9 pM. The nanosensor was selective for albumin in the presence of transferrin and hemoglobin (Esentürk et al. 2019).

Hallaj and group developed nitrogen and phosphorus-co-doped CDs as a dual mode colorimetric and fluorimetric nanosensor for the detection of uric acid. The nanosensor was based on the *in situ* formation of silver shell on gold nanoparticles and IFE. The addition of gold nanoparticles quenches the fluorescence intensity of nitrogen and phosphorus-co-doped CDs because of the overlap between the emission peak of nitrogen and phosphorus-co-doped CDs and the SPR peak of gold nanoparticles. On addition of Ag^+ and uric acid, the SPR peak intensity increases because of the reduction of Ag^+ to Ag^0 and Ag shell formation on the surface of gold nanoparticles. A higher concentration of uric acid further led to a blue shift in the SPR peak position of gold nanoparticles. The change in the intensity of the SPR peak and position caused more fluorescence quenching of nitrogen and phosphorus-co-doped CDs because of enhanced spectral overlap between silver-attached gold nanoparticles and nitrogen and phosphorus-co-doped CDs (Hallaj jhet al. 2021).

Detection of Molecules or Phenomena indicative of Disease

Optical nanosensors may also be utilized to detect certain molecules (glutathione, cytochrome C, cysteine, alkaline phosphatase, etc.) that serve as biomarkers of a particular disease and even to monitor certain phenomena (pH, oxidative stress) which may be indicative of a particular disease as given below.

pH

Intracellular pH is linked with cellular behavior and pathology of diseases such as cancer and neurodegenerative diseases. Fluorescent semiconductor polymer dots are beneficial for pH detection owing to their excellent single-particle brightness, good photostability, and low cytotoxicity, which facilitates cellular imaging and detection. Chen et al. developed dual emission semiconductor polymer dots by cross-linking poly(9,9-dioctylfluorenyl-2,7-diyl) (PFO), which is insensitive to pH and fluorescein isothiocyanate (FITC) which is pH sensitive using poly (styrene-co-maleic anhydride) as a cross-linker. Emission peaks of PFO remain unchanged with variation in pH from 3 to 8, whereas the emission peak of FITC increased. Thus, the fluorescence signal of FITC at 517 nm was selected as the response signal, and the fluorescence signal of PFO at 439 nm was selected as the reference signal. However, the signal of FITC was weak, and hence poly[(9,9-dioctyl-fluorenyl-2,7-diyl)-co-(1,4-benzo-{2,1′,3}-thiadazole)], a polymer dye having similar emission wavelength as FITC was introduced. The new polymer dots had a size of 5.2 nm. The system's emission intensity ratio (I_{517}/I_{439}) varied linearly with respect to pH in the range of pH 3.0 to 8.0. The developed polymer dots also showed reversibility and stability in the estimation of pH measurement. They were successfully internalized into Hela cells (Chen et al. 2019).

Shen et al. developed organelle-targeted SERS nanosensors for detecting pH in organelles like the nucleus and mitochondrion. Gold nanorods were functionalized with MPy as a pH-responsive molecule. Targeting nanosensors to the nuclear and mitochondrial organelles was achieved via conjugating the gold nanorods with nuclear localization signal peptide and mitochondrial localization signal peptide respectively. Super-high resolution fluorescence imaging and bio-transmission electron microscopic methods confirmed the localization of the developed nanosensors in the desired organelles (Shen et al. 2018).

Zheng et al. designed a cell-penetrating peptide conjugated dual fluorescent and SERS nanosensor for *in-situ* intracellular pH imaging of single living cells during the cell cycle. MPy was employed as the pH-responsive element and conjugated to gold nanoparticles. These were then conjugated with TAT peptide (a cationic peptide widely used for promoting cellular internalization of nanosensors), and TAMRA, a fluorescent probe, was further conjugated with TAT peptide. The nanosensor was successfully utilized to monitor pH changes happening throughout the cell cycle, namely alkalization and acidification correlating with the processes and species involved in energy storage and usage in the cell (Zheng et al. 2019).

Oxidative Stress

Oxidative stress can be defined as a state of imbalance between the antioxidant defense system and the generation of ROS, which leads to different diseases such as cancer, diabetes, cardiovascular diseases, etc. H_2O_2 is an important biomarker of oxidative stress. Garg et al. developed lysine-functionalized tungsten disulfide quantum dots for optical detection of H_2O_2. The quantum dots were found to act as a substitute for peroxidase enzyme and could convert 3,3′,5,5′-tetramethylbenzidine into a blue-colored compound in the presence of H_2O_2. The developed nanosensors could detect H_2O_2 in the 0.1 to 60 μM range within five minutes. The usage of enzymes requires specific storage conditions to preserve their activity. The method is beneficial since it can mimic the action of the peroxidase enzyme and thus can act as a substitute for it (Garg et al. 2020).

Hydroxyl radicals (•OH) are ROS whose overaccumulation has been found in cardiovascular disease, cancer, and neurological disorders. Qu et al. developed fluorescence and SERS dual-mode nanosensors to detect •OH. They immobilized single-stranded DNA labeled with amino groups at the 3′ end onto gold nanoparticles. Further, complementary strands labeled with Alexa Fluor 488 were immobilized onto gold nanoparticles via hybridization. Gold nanoparticles cause fluorescent quenching of Alexa Fluor 488 and function as SERS substrates. Cleavage of DNA strands by •OH causes the release of Alexa Fluor 488 from the surface, restoring the fluorescence of Alexa Fluor 488. The developed nanosensors showed a LOD of 10 nM for •OH detection. After exposure to a free radical initiator, the nanosensor was successfully applied to detect •OH released by human bronchial epithelial cells and A549 cells (Qu et al. 2017).

Shen et al. developed interference-free SERS nanoprobes for real-time *in situ* detection of intracellular ROS in the mitochondrion, which would facilitate a better understanding of the mechanism of photothermal therapy. 4-mercaptobenzonitrile (MBN) was used as the Raman reporter since it shows a sharp and robust peak (nitrile vibration) in the cellular Raman-silent region (1800–2800 cm^{-1}) to eliminate any interference from cellular contents. Shen et al. used an Au-Ag core-shell structure in which MBN was conjugated to the Au-core. The surface of the nanoprobes was further modified with mitochondrion targeting peptide. Once the nanoprobe enters the mitochondrion, the release of ROS will etch the Ag shell, causing a decrease in the SERS signal (Shen et al. 2019).

Glutathione

Glutathione is a powerful antioxidant in our body. Aberrant glutathione levels are associated with disease states such as cancer, diabetes,

Alzheimer's disease, etc. Han et al. developed polymer dots having a solid green fluorescence by self-oxidation and auto-polymerization with hydroquinone and ethylenediamine as precursors. MnO_2 nanosheets were employed to detect glutathione and induce fluorescence quenching in the system. The overlapping UV-visible absorption spectrum of MnO_2 nanosheets with the excitation spectrum of polymer dots induces quenching of fluorescence of the latter. When the nanosensor comes in contact with glutathione, MnO_2 nanosheets are broken down, causing the conversion of MnO_2 to Mn^{2+} and simultaneous recovery of fluorescence of polymer dots. The developed nanosensor demonstrated good selectivity towards the detection of glutathione, broad linearity ranging from 0.5 to 200 μM, LOD of 0.1 μM, and could successfully detect glutathione in human serum samples (Han et al. 2018).

Cytokine

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine. Increased blood levels of TNF-α have been shown to cause cardiovascular diseases, psoriasis, Alzheimer's disease, rheumatoid arthritis, cancer, and inflammatory bowel disease. Gholami and group developed a SERS quenching nanosensor to quantify TNF-α in blood. They loaded benzothiazole dye (E)-1-((6-methoxybenzo[d]thiazole-2-yl)diazenyl) naphthalene-2,6-diol (BAN) as a Raman reporter onto the SERS substrate. TNF- α was selectively extracted from blood plasma, and its disulfide bond was reduced, followed by exposure to BAN-modified SERS substrate. This causes quenching of the Raman signal of BAN as a result of displacement of BAN from the SERS substrate by the disulfide-reduced TNF-α. The method could quantify TNF-α at levels as low as 0.17 pg/ml. Cross-validation of the SERS quenching nano sensor against ELISA revealed a percent agreement of 93.39% between the two techniques (Gholami et al. 2020)

Serotonin

Serotonin, also known as 5-hydroxytryptamine, is an important neurotransmitter involved in temperature regulation, contraction of muscles, mood, sleep, endocrine regulation, etc. Wang et al. developed Mn^{2+} doped ZnS quantum dots embedded in silica nanoparticles within a molecular imprinted polymer matrix for selective detection of serotonin. When the nanosensor is exposed to serotonin, serotonin binds to the cavities and interacts with amino groups on the quantum dots, which induces the quenching of fluorescence quantum dots. The developed nanosensor showed excellent selectivity and sensitivity and was able to detect serotonin in human serum within a short period (Wang et al. 2018).

Sha et al. fabricated fluorescence turn-on gold nanoclusters encapsulating transferrin using microwave radiation to detect serotonin. When the nanoclusters were exposed to serotonin, there was aggregation-augmented emission of transferrin-loaded gold nanoclusters due to the interaction of serotonin with sialic acid fragments of transferrin. The nanosensor showed good selectivity, an LOD of 0.049 μM, and could detect serotonin in human serum (Sha et al. 2019).

Chavez et al. developed aptamer-conjugated gold nanoparticles for the detection of serotonin. Aptamer for serotonin was adsorbed onto gold nanoparticles. The developed aptamer-gold conjugates undergo aggregation when exposed to salt such as NaCl. However, binding serotonin to the nanosensor enhances the stability of the aptamer-gold conjugates against aggregation by inducing a change in aptamer conformation, thereby improving the aptamer's affinity for the gold nanoparticles. The key features of the developed nanosensor included the utilization of minimum sample quantity (10 μL), quick response time (< 15 min), and a colorimetric output that is easy to interpret and can be integrated with smartphones or tablets for point-of-care diagnostics (Chávez et al. 2017).

Cytochrome c

Detection of cytochrome c at the subcellular level in living cells can serve as an indicator of the involvement of mitochondria in apoptosis. Amin et al. designed a nanosensor based on cadmium-telluride quantum dots capped with thioglycolic acid for fluorescent detection of cytochrome c levels in cells. On exposure to increasing cytochrome c concentrations, the nanosensor showed decreased fluorescence. Photoinduced electron transfer from the excited quantum dots to oxidized cytochrome c causes quenching of fluorescence of the quantum dots (Amin et al. 2017).

Zhang et al. fabricated dual SERS and fluorescence-based nanosensors based on gold nanotriangles to detect cytochrome c. The usage of nanotriangles offers several benefits. Firstly, they are anisotropic, show broad plasma resonance from the visible to the IR region, and have high sensitivity because of their strong LSPR effect. Secondly, the size of these gold nanotriangles between 30–100 nm permits easy ingress into cells and avoids phagocytosis. Aptamer specific for cytochrome c was modified onto gold nanotriangles via Au-S bond, and complementary strands connected with Cy5 were then complementarily paired with aptamer-modified gold triangles via DNA hybridization. Cy5 is a Raman and fluorescent reporter. When these nanosensors enter normal cells, they function as Raman-enhanced substrates to enhance the Raman signal of Cy5 and quench the fluorescence of Cy5. When the cells undergo apoptosis on exposure to aflatoxin B1, the cytochrome c translocated from the mitochondria

into the cytoplasm and bound to its aptamer causing detachment of the complementary chains from Cy5. The distance between the complementary chains and the gold nanotriangles increased, causing the weakening of the Raman signal of Cy5 and restoring the fluorescent signal of Cy5. The nanosensors demonstrated good sensitivity and selectivity for real-time monitoring of cytochrome translocation from the mitochondria into the cytoplasm and accurate quantification of intracellular cytochrome c levels (Zhang et al. 2019).

Cysteine

Cysteine is present in micromolar to millimolar concentrations in human plasma. Excess amounts of cysteine can cause neuronal damage. Hai et al. developed a nanosensor for the colorimetric detection of cysteine. The nanocomposite comprised gold nanoparticles coated with reduced graphene quantum dots followed by adsorption with Ag^{+}. The nanocomposite showed a SPR band at 525 nm. When the nanocomposite comes in contact with cysteine, cysteine interacts with adsorbed Ag^{+} and induces cross-linking, causing aggregation of nanocomposite changing its color. The nanocomposite exhibited high selectivity for cysteine against glutathione which commonly interferes with cysteine estimation (Hai et al. 2018).

Vitamins

Deficiency of vitamin A can cause night blindness whereas excess of vitamin A causes low bone mass and osteoporosis. Safari and the group reported zinc sulfide quantum dots for detecting vitamin A. When the quantum dots come in contact with vitamin A, photoinduced charge transfer from the former to the latter causes fluorescent quenching. The nanosensor showed the ability to detect vitamin A in the presence of interfering compounds such as vitamins (B_2, B_6, E, K, H, D_3, and C) and cations (Na^{+}, Fe^{2+}, Mg^{2+}, Ca^{2+}, Cu^{2+}, and NH^{4+} ions) (Safari et al. 2020). Deficiency of folic acid may cause anemia whereas excess folic acid may cause zinc deficiency, anorexia, nausea, and gastrointestinal syndrome. Zhang et al. developed a nanosensor based on CDs to detect folic acid. Binding folic acid to the CDs resulted in fluorescence quenching due to the IFE. The nanosensor was successfully utilized for the analysis of human urine samples (Zhang W et al. 2020).

Alkaline Phosphatase

Abnormal levels of alkaline phosphatase in serum indicate bone disease, liver problems, breast and prostate cancer, and diabetes. Zhao et al. developed a nanosensor based on ratiometric fluorescence to detect

alkaline phosphatase in serum. Phosphorylated fluorescein molecules were covalently immobilized onto polyethylene terephthalate nanofibers, and bis quaternary ammonium salt of tetraphenylethene (TPE-$2N^+$) was electrically adsorbed onto the surface of these fibers. The sensor showed blue fluorescence at 471 nm due to complexation between phosphorylated fluorescein and TPE-$2N^+$ causing aggregation-induced TPE emission. When the nanosensor is exposed to alkaline phosphatase, the phosphodiester gets hydrolyzed, causing an increase in fluorescence emission at 514 nm due to fluorescent recovery of fluorescein and a decrease in fluorescence emission of TPE at 471 nm, causing a color change from blue to green when observed under a UV lamp (Zhao et al. 2017).

Drug Assays in Pharmaceutical Dosage Forms

Optical nanosensors have also been explored for assaying drug content in pharmaceutical dosage forms as given below.

Azizi et al. fabricated CDs using a green technology-based technique with zein biopolymer as a carbon source. They functionalized these CDs with 3,5-dinitro benzoyl chloride (DNB) for selective detection of sumatriptan in pharmaceutical dosage forms and urine samples. When these CDs functionalized with DNB are exposed to sumatriptan, fluorescence quenching occurs. The developed nanosensors showed an LOD of 0.32 nM (Azizi et al. 2019). Ding et al. designed CDs for the detection of vitamin B_{12}. When the CDs are exposed to vitamin B_{12}, there is a perfect overlap between the absorption band of vitamin B_{12} and the excitation band of CDs causing quenching of the fluorescence of CDs via IFE. The nanosensor showed good sensitivity and selectivity for estimating vitamin B_{12} in injectables (Ding et al. 2018).

Detection of Drug Abuse

Recent years have witnessed a surge in the abuse of illicit drugs such as cocaine, amphetamine, morphine, etc. (Chen C H et al. 2020). Optical nanosensors have been used to detect illicit drugs like morphine and amphetamine as given below.

Masteri-Farahani et al. developed an optical nanosensor based on CdS quantum dots functionalized with anti-morphine antibodies to detect morphine. When the CdS quantum dots are functionalized with an anti-morphine antibody, the fluorescence signal of the former is quenched due to FRET. However, when the nanosensor is exposed to morphine, the interaction between the anti-morphine antibody and morphine causes the restoration of fluorescence of CdS quantum dots. The nanosensor could selectively detect morphine in the presence of methamphetamine (Masteri-Farahani et al. 2018).

Molecular imprinted polymer technology is a promising option to enhance the selectivity of quantum dots-based nanosensors. It involves developing nanosensors embedded within a polymer that has cavities to recognize particular analytes selectively. This technology offers excellent affinity and selectivity, and is also economical. Masteri-Farahani et al. designed a nanosensor integrating molecularly imprinted polymer technology and graphene quantum dots to detect methamphetamine. The binding of methamphetamine to the quantum dots causes fluorescence quenching via energy transfer from graphene quantum dots to methamphetamine. Hydrogen bonding occurs between carboxylic acid groups on the surface of graphene quantum dots and methamphetamine (Masteri-Farahani et al. 2020).

Therapeutic Drug Monitoring and Therapeutic Efficacy Monitoring

Therapeutic drug monitoring involves the assessment of drug levels in the body for drugs having a narrow therapeutic index (Garzón et al. 2019). Therapeutic efficacy monitoring involves measuring the response to a particular treatment, for example, anticancer therapy (Bhattacharya et al. 2019). Optical nanosensors have been used in therapeutic drug monitoring and therapeutic efficacy monitoring as given below.

Erlotinib is a drug used for non-small cell lung cancer and pancreatic cancer. It requires therapeutic monitoring owing to its narrow therapeutic index and high inter-patient response variation. Erlotinib possesses an alkyne group that can be utilized for click chemistry reactions with an azide group. Litti et al. synthesized gold nanoparticles using the laser ablation synthesis in solution technique and functionalized them with an azide group. The developed nanosensor enabled the detection of erlotinib at nanomolar concentrations in spiked plasma samples. The nanosensor was based on the competitive reaction between erlotinib and propynyl fluorescent red (PFR) for azide groups on the surface of gold nanoparticles. A good correlation was seen between increasing concentration of erlotinib and decreasing SERS signal intensity of PFR (Litti et al. 2019). Overdosing of heparin is known to cause thrombocytopenia or hemorrhage. Hence, monitoring serum levels of heparin during clinical usage and the postoperative treatment period is critical. Zhu et al. developed a dual fluorimetric-colorimetric nanosensor to detect heparin using neutral red and up-conversion nanoparticles. They also developed a portable intelligent phone sensing platform based on 3D printing. The platform comprised a sampling slot for fixing a cuvette, dark cavity, 980 nm laser, and a smartphone (iPhone 8 Plus). Initially, the nanosensor solution was added to the cuvette, incorporating different concentrations of heparin. The up-conversion luminescence was obtained through the smartphone

and was further broken down into RGB values to attain quantitative detection using an installed color recognition application. When the nanosensor comes in contact with heparin, it causes fading of neutral red and recovery of the quenched up-conversion fluorescence. The nanosensor showed a LOD of 0.1 nM in fluorescent mode and 0.3 nM in colorimetric mode (Zhu et al. 2021).

In situ monitoring of intracellular matrix metalloproteinase-2 (MMP-2) enzyme levels has a cardinal role in early cancer diagnosis and therapeutic monitoring of cancer. Zhang et al. designed an MMP-2 responsive nano sensor wherein they incorporated BHQ-3 into the inner walls of mesopores of mesoporous silica nanoparticles, and fluorescent dye Cy5 was loaded in the pores of the nanoparticles. Anti-MMP-2 antibody was utilized as a bio-lid onto the mesoporous silica nanosensor by electrostatic interactions between amine-functionalized mesoporous silica nanoparticles and negatively charged anti-MMP-2 antibody. Aminopropyl groups on the walls of the pores were covalently linked with BHQ-3. When there is no MMP-2, the nanosensor is in a 'fluorescence off' state due to the quenching of Cy 5 by BHQ-3. However, when the nanosensor is exposed to MMP-2, the bio-lid gets removed opening the mesopores, and Cy5 release causes fluorescence. The nanosensor enabled sensitive *in situ* monitoring of intracellular MMP-2 and was also helpful in tracking the change in intracellular MMP-2 levels on treatment with MMP-2-repressive drug (Zhang et al. 2018).

Theranostics

The field of theranostics is an upcoming application of nanotechnology, coupling the functions of diagnosis and therapy within a single platform (Vo-Dinh et al. 2015). Theranostics promotes therapeutic efficacy monitoring, enhances therapeutic outcomes, and eliminates adverse effects (Shetty et al. 2019). Theranostic nanocarriers using optical sensing have been explored in cancer, infections, inflammation, and wound healing as given below.

Photothermal therapy involves the conversion of light into heat for thermal destruction of cancer cells. Photodynamic therapy (PDT) involves the generation of ROS on exposure to light for destroying cancer cells. Zheng et al. developed a multifunctional theranostic system for cancer imaging and therapy. They first modified hypocrellin B with 1,2-diamino-2-methyl propane to form NIR light-responsive amino-substituted hypocrellin. This derivative showed broad absorption in the 400–800 nm range, maximum NIR emission at 710 nm, and excellent singlet oxygen yield on exposure to NIR light. They then prepared biodegradable nanovesicles of this modified hypocrellin B with poly(ethylene glycol)-b-poly(lactic-co-glycolic acid) (PEG-PLGA) using a self-assembly technique.

The nanovesicles enable both fluorescent and photoacoustic imaging. *In vitro* and *in vivo* studies proved that the developed nanovesicles had excellent photothermal stability, improved tumor accumulation, and the desired biodegradation rate. Thus, the developed system enabled simultaneous fluorescent/photoacoustic imaging of cancer cells and synergistic photodynamic and photothermal therapy (Zheng et al. 2018).

Li et al. designed novel theranostic nanoparticles via the self-assembly of epirubicin (chemotherapeutic drug) and indocyanine green (photothermal agent). Epirubicin and indocyanine green could self-assemble into molecular nanoparticles via electrostatic, π-π stacking, and hydrophobic interactions. The nanoparticles enabled dual imaging via NIRF and photoacoustic imaging, and showed pH-responsive and photo-responsive drug release. The developed theranostic system facilitated good tumor targeting with excellent spatial resolution and penetration depth. The nanocarriers showed good synergistic chemotherapeutic and photothermal destruction of tumor cells (Li et al. 2017).

Xu et al. developed a self-illuminating nanoparticle for imaging of inflammation and cancer treatment based on Ce6-luminol-PEG conjugate capable of bioluminescence resonance energy transfer (BRET). Chlorin e6 served as a photosensitizer. The conjugate undergoes self-assembly to form a core-shell micellar nanostructure. When exposed to oxidative conditions with surplus ROS and myeloperoxidase, the *in situ* bioluminescence of luminol excites the photosensitizer Ce6 to generate fluorescence and singlet oxygen $^1O_2$ via BRET, thus facilitating imaging of inflammation and tumor PDT (Xu et al. 2019).

Germanene is a two-dimensional nanoelemental xene that has good stability and photothermal activity. Its fabrication in the form of nanosheets enables high drug loading. Feng et al. developed germanene-based theranostic as an intelligent surgical adjuvant therapy for solid tumors to inhibit tumor recurrence and wound infection. The germanene-based nanosheets showed good drug loading for doxorubicin. The nanosheets exhibited pH-responsive and NIR-responsive drug release at the tumor site. The nanosheets were loaded in a hydrogel matrix comprising agarose and chitosan. The hydrogel can be coated on the postoperative wound surface after tumor removal. After exposure to NIR radiation, local hyperthermia-induced bacterial destruction, and NIR-induced release of doxorubicin enable residual tumor ablation. The developed nano platform enables multimodal imaging-guided treatment since the material possesses dual fluorescent and photoacoustic imaging (Feng et al. 2020).

Zhou et al. developed an intelligent photo-responsive antibacterial wound dressing for the simultaneous detection and treatment of bacterial infections to expedite the process of wound healing. The system could sense the presence of pathogenic bacteria to ensure controlled delivery of photosensitive agents and show a colorimetric response in the event

of an infection. Tryptophan-modified thiophene aldehyde was used as the photosensitizer to improve the aqueous solubility and decrease the phototoxicity of trithiophene aldehyde. Amine groups from water-soluble carboxymethyl chitosan and aldehyde from oxidized carboxymethyl cellulose were cross-linked via Schiff base reaction to form a covalent hydrogel dressing. Photosensitizer-loaded vesicles were included in the gel network. 4-methylumbelliferyl-α-D-glucopyranoside acid (MUD) was grafted onto the surface of the wound dressing. Enzymes exuded by pathogenic bacteria break down MUD, causing cleavage of the fluorophore 4-methylumbelliferone and its subsequent release into the hydrogel network, which emits blue light under UV light. Cytotoxin produced by pathogenic bacteria lyses the vesicles to release the photosensitizer. The vesicles were selectively responsive to pathogenic *Pseudomonas aeruginosa* and *Staphylococcus aureus* versus non-pathogenic *Escherichia coli* species (Zhou et al. 2020).

Wu et al. developed a theranostic wound dressing for visible monitoring of H_2O_2 and promotion of the wound healing process. The presence of inflammation or infection in the wound would cause high levels of H_2O_2, which could preclude wound healing. Thus, it would be beneficial to track the levels of H_2O_2 as an indicator of wound healing status. Wu et al. used europium (III) coordination polymers as H_2O_2 sensing probes and loaded them within polyacrylonitrile nanofibers. The system monitored H_2O_2 levels in the wound via a visible color change. The nanofibers promoted wound healing via the facilitation of neovascularization, as evidenced in an animal model. The 3-dimensional network of electrospun polyacrylonitrile nanofibers also aided cellular adhesion and migration to foster wound healing. The developed system holds promising potential in knowing the status of the wound microenvironment and decreasing the frequency of wound dressings which would ultimately translate into lower costs and better patient compliance (Wu et al. 2020).

Jin et al. developed a theranostic platform for dual fluorescent imaging and PDT of infectious endophthalmitis. Toluidine blue was employed as a photosensitizer loaded onto UiO-66-NH_2 nanoparticles. The developed nanoparticles exhibited pH-sensitive release with faster release at pH 5.5 (acidic microenvironment of bacterial infections) than at pH 7.4. The breakdown of UiO-66-NH_2 nanoparticles yields zirconium ions which aid in curbing bacterial growth by disrupting the bacterial cell wall. Lipopolysaccharide-targeting polypeptide (PEP) and PEG were grafted onto UiO-66-NH_2 nanoparticles to achieve targeting toward bacterial cell wall and to escape uptake by immune cells respectively (Fig. 4).

The developed theranostic system enabled self-imaging, biofilm removal, and sterilization of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* (Jin et al. 2020).

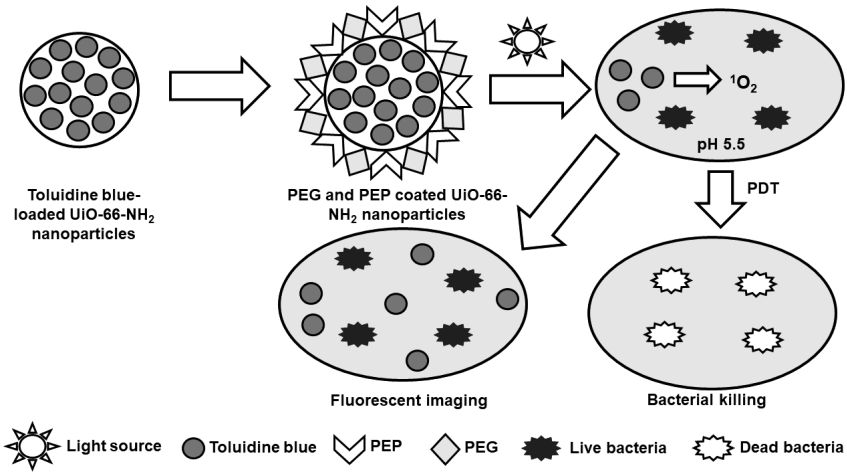

Fig. 4. Schematic diagram of a theranostic platform for dual fluorescent imaging and photodynamic therapy of infectious endophthalmitis. ⏎

Liao et al. developed a theranostic platform loaded with rifampicin for early diagnosis and treatment of tuberculosis. The developed nano platform was based on aggregation–induced emission (AIE) and was capable of localization in granuloma and releasing fluorescent signals for early diagnosis of tuberculosis. The group used 2-(2,6-bis((E)-4-(phenyl(4′-(1,2,2-triphenylvinyl)-[1,1′-biphenyl]-4-yl)amino)styryl)-4H-pyran-4-ylidene)malononitrile as an AIE-based fluorophore and photosensitizer. The developed nanocarrier could enter the granulomas through the Enhanced Permeability and Retention effect after intravenous injection and produce bright red fluorescence after excitation with light. Photoexcitation also triggered the release of ROS and rifampicin for synergistic destruction of bacteria causing tuberculosis (Liao et al. 2020).

Zhou et al. developed silica-encapsulated silver-coated gold nanoparticles. They conjugated them with 2,3-naphthalocyanine dihydroxide (Nc) and vancomycin to form multifunctional nanoparticles for SERS imaging and PDT of vancomycin-resistant *Enterococci* strains. 2,3-naphthalocyanine dihydroxide (Nc) acted as a photosensitizer. Silver-coated gold nanoparticles act as the SERS active core, and the system showed good selective binding to vancomycin-resistant *Enterococci. In-vitro* photodynamic studies showed that the nanoparticles at nanomolar concentration could cause a 4-5 log reduction in vancomycin-resistant *Enterococci* (Zhou et al. 2018).

Ma et al. designed a theranostic nanocarrier for inflammation. Prednisolone, an anti-inflammatory drug, was connected to the two-photon aggregation-induced emission fluorophore TP via a ROS-reactive linkage to form TPP. This TPP is then incorporated into an amphipathic

diblock copolymer poly(2-methacryloyloxyethyl phosphorylcholine)–poly(2-methylthioethanol methacrylate) (PMPC–PMEMA) to form micelles. Once administered, the micelles (57.5 nm in size) can accumulate at the inflammatory site owing to the leaky clearance of inflamed tissue. At the site of inflammation, oxidative stress triggers a series of reactions. Firstly, the PMEMA block becomes hydrophilic due to ROS disrupting the micellar structure, releasing encapsulated TPP. When TPP is exposed to ROS in the inflammatory microenvironment, the ROS-reactive linkage connecting prednisolone and TP is cleaved, thus releasing free prednisolone. The developed theranostic system showed good utility in murine models of acute lung injury, atherosclerosis, and arthritis (Ma et al. 2020).

Zhao et al. developed NIR light-responsive molybdenum disulfide nanosheets loaded with dexamethasone for intra-articular therapy of osteoarthritis. Intraarticular injection of the developed formulation, when combined with NIR radiation, enhanced the therapeutic efficacy of dexamethasone at low doses. The molybdenum disulfide nanosheets further enabled photoacoustic imaging. The developed formulation ensured prolonged retention of dexamethasone in the joint cavity. The nanoformulation showed good responsiveness to NIR radiation *in vitro* and *in vivo* and can modulate drug release via photothermal conversion (Zhao et al. 2019).

Conclusion

Optical nanosensors are anticipated to grow in the healthcare and biomedical sectors. They have been fabricated using a variety of materials including organic, inorganic, and composites. They can contribute immensely to disease detection, detection of drug abuse, therapeutic drug monitoring, analysis of pharmaceutical dosage forms, and theranostics. Their ability to provide sensitive, selective, accurate, and portable nanosensors enables their application in personalized medicine and also in remote areas and developing countries. The thrust areas in research include enhancing selectivity and sensitivity, reducing the response time, and enabling multiplexed analysis. The design of optical nanosensors is influenced by their end-use. The possibility of using various optical principles and different materials for nanosensor fabrication makes them suitable for versatile applications. They can be used for simple and cost-effective detection of a single molecule or multiplexed detection in a complex sample matrix. Composite optical nanosensors combining fluorescence with SERS are promising for rapid and sensitive multiplexed quantitative analysis. It is important to consider cross-reactivity when developing nanosensors for multiplexed detection.

However, there are certain issues associated with optical nanosensors. Manufacturing of optical nanosensors involves using expensive equipment and high-precision fabrication techniques to generate highly selective and sensitive nanosensors. Fluorescent nanoprobes are extremely expensive. Further, few fluorescent detection kits may require fresh preparation of assay reagents. The cost of production needs to be kept in check to ensure that the sensors are affordable and can compete with existing sensing technologies. It is challenging to produce stable optical nanosensors that can withstand environmental conditions of temperature and humidity and produce consistent results. Optical nanosensors are likely to face regulatory challenges due to their novel nature and potential safety concerns. *In vivo* application of optical nanosensors requires detailed studies on the cytotoxicity, metabolism, biodistribution, and toxicity of these materials. Nanomaterial synthesis may generate toxic by-products thereby endangering terrestrial and aquatic life. Obtaining regulatory approval can be a long and expensive process, which can delay or impede the commercialization of the sensors.

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4

The Evolving Landscape of Magnetic Nanosensor Usage

Recent Developments and Promising Opportunities

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Introduction

Over the last few decades, there has been a growing interest in the controlled delivery of therapeutic agents, providing a major boost to the arena of nanomedicine. Magnetic nanosensors present an exciting opportunity for targeted delivery, owing to key benefits including the possibility of higher drug loading and a unique blend of magnetic and biological properties (Vangijzegem et al. 2019). These devices are most commonly loaded with magnetic nanoparticles (MNPs) (with diameters ranging from 5 to 300 nm) and magnetic particles (with a greater diameter from 300 to 5,000 nm), which have found applications in conjunction with biosensors. This functionalization has found widespread potentials for use across industries (Koh and Josephson 2009), which shall be explored in detail over the course of this chapter.

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Functionalized magnetic nanomaterials have recently gained research interest in the agricultural industry. They are chiefly utilized for the purpose of biosensing and may be harnessed for the monitoring of environmental pH, levels of pollutants such as fertilizers, and detection of heavy metals in water run-off (Yang et al. 2021). The low toxicity, relatively greater compatibility as compared to other nanosystems, and stability has poised them as an affordable and versatile monitoring strategy in agricultural sciences (Bhat et al. 2022).

A study undertaken by Hojjati-Najafabadi and co-workers, explored the usage of magnetic nanosensors in monitoring the levels of potentially dangerous pollutants in various water resources. In this study as well, the low toxicity, ease of preparation and satisfactory conductivity of magnetic nanosensors is highlighted, expanding the avenues for their usage (Hojjati-Najafabadi et al. 2022). Magnetic nanosensors have also been used to overcome the limitations of spectroscopic techniques such as surface-enhanced Raman scattering (SERS). Zhang and colleagues explored the potentials of nanosponges loaded with MNPs to enhance the efficiency of removal of organic pollutants, which may be applied across various disciplines (Zhang et al. 2021)

As for the pharmacological applications of magnetic nanosensors, these devices have been utilized to enhance the sensitivity and reliability of test results, in comparison with conventionally used, more traditional methods of diagnosis. A key advantage offered is the improved stability and increased circulating half-life, also permitting the monitoring of therapy over extended periods. Pant and co-researchers monitored the magnetic resonance properties of nanosensors, for the assessment of key protein biomarkers involved in the pathogenesis of sepsis (Pant et al. 2021). Banerjee and co-workers explored the applications of functional magnetic nanosensors in determining the differentiation and cross-reactivity between dengue and zika viruses, with high sensitivity and reproducibility (Banerjee et al. 2021). Moving forward, these systems may be employed for the detection of a greater diversity of pathogens.

In addition to understanding the advantages and challenges associated with the usage of magnetic nanosensors, it is essential to understand those linked with MNPs, as a strategy to improve outcomes. These agents have been gaining attention recently, owing to the reduced dose requirements, improved bioavailability and lowered potentials for systemic toxicity (Ghosal et al. 2022). A significant contribution has been the highly sensitive and reproducible detection of inter-cellular ions, enabling robust monitoring (Lei et al. 2018). As these systems continue to be developed and studied, a combination of analytical techniques may be used to facilitate detection.

A major limitation associated with the usage of magnetic nanosensors is the loss of efficacy, following the removal of an external magnetic field.

In addition to this, their benefits have been largely evaluated *in vitro*, and translation to biological systems may be complicated by the difficulty in maintenance of three dimensional action (Schneider-Futschik and Reyes-Ortega 2021). Another challenge associated with MNPs is the maintenance of stability, which further impacts their action in living systems (Jeon et al. 2021). In the sections that follow, various key principles of detection have been discussed, alongside recent applications and results to support their usage.

Principle of Sensing and Types of Magnetic Nanosensors

MNPs are synthesized using a variety of methods, including but not limited to hydrothermal synthesis, formation of a microemulsion and decomposition at high temperatures (Ghosal et al. 2022). This is followed by enveloping the synthesized nanoparticles (NPs) with a polymer coat and introducing a linking group. Various ligands and biomolecules such as peptides and antigens may serve as linking groups. This step is essential to ensure the functionalization of the NPs into nanosensors (Doswald et al. 2019).

Over time, various sensing theories have been proposed to shed light on the principle of the sensing ability of these nanosensors. The principle of magnetic permeability is commonly applied to distinguish between MNPs and those lacking magnetic properties. By recording the inductance of a sample placed into a coil, the degree of movement of the NPs into the sample may be utilized for the bioassay of a variety of molecules. The measurement of the permeability of these agents into the sample and their subsequent binding capacity, measured after multiple washings, provides an insight into their functioning principle, which is chiefly binding to targets (Schrittwieser et al. 2016).

In addition to this, obtaining an understanding of the hydrodynamic properties of these agents may be useful in understanding their principle of working. When introduced into a sample, these nanosensors recognize the analyte molecules and are seen to undergo aggregation around them. This, in turn, modulates their hydrodynamic properties, and this change may be measured suitably, by the usage of magnetic fields (Martchenko et al. 2011).

Magnetic nanosensors may be studied under two broad headings that are centered around their physical mechanism of action. This includes nanosensors working by measurement of electric current, and those recording magnetism. Magnetic nanosensors relying on the measurement of electrical current have been observed to undergo a loss in current, following analyte adsorption. This phenomenon has been chiefly attributed to changes in the coating of NPs, which inhibits energy transfer. Magnetic nanosensors relying on electrical current measurement have

been utilized widely in the detection and monitoring of glucose oxidase, as well as other oxidase enzymes (Lim and Ramakrishna 2006). They have achieved this by developing carbon nanotubes.

As for the detection of magnetism, nanosensors utilized in imaging, largely function on the principle of spin-spin relaxation time (represented as T2). This is a unique parameter and is harnessed to distinguish between different types of tissues. When NPs comprising these nanosensors bind to their desired biological targets, they bring about a reduction in T2 levels of surrounding tissues, enabling more sensitive detection (Noginova et al. 2009).

Ta and co-workers explored the usage of magnetic resonance nanosensors in the detection of thrombosis. Using a peptide to target the thrombus and a fluorescent dye to facilitate imaging, the nanosensors facilitated differentiation between old and new clots, based on the intensity of the signal produced (Ta 2018). Over time, there has been a growing interest in the applications of magnetic nanosensors, especially in the biomedical applications. Table 1 offers an overview of the recent applications, the principle employed, and future perspectives of magnetic nanosensors.

Factors Affecting the Performance of Magnetic Sensors

Type of Materials Used

In ferromagnetic materials (such as iron, nickel, cobalt), the magnetic moment of the metals aligns along the direction of the magnetic field generating a huge magnetic moment. They show a slight residual magnetic moment even after the removal of the magnetic field. Paramagnetic materials show magnetic moment due to the presence of an unpaired electron but have no magnetic domains. Examples of paramagnetic substances include magnesium, tantalum, lithium, and gadolinium. When placed in magnetic fields, their moments align with the field; however, they do not retain any magnetic moment once the applied field is removed. Materials such as copper, gold, silver and many other known elements that have no unpaired electrons and possess zero magnetic moment, are referred to as diamagnetic substances. They display very weak responses generally due to realignment of electron orbits in the applied magnetic field. Like paramagnetic substances, they do not retain any magnetic moment once the applied field is removed as well (Issa et al. 2013).

Antiferromagnetic substances and ferrimagnetic materials are compounds with their atoms residing at different lattice positions. In antiferromagnetic substances, the two atoms have their magnetic moments in opposite direction and as a result, their net magnetic moment is zero (examples include MnO, CoO, NiO, $CuCl_2$). In ferrimagnetic substances

Table 1. Highlights of the recent applications of magnetic nanosenors, the sensing principle employed, application and scope for future use. ⏎

Application of magnetic nanosensors	Composition of nanosensors	Biomolecule detected	Brief overview of sensing principle	Future perspectives and scope for application	References
Usage of MRI for chemical detection	Acetylcholine-catalyzing enzymes, contrast agents sensitive to pH	Acetylcholine	Triggering of enzymatic hydrolysis, lowering of surrounding pH and changes in the relaxation time of the nanoparticles.	CNS imaging, further insight into brain functioning and pharmacological potentials of neurotransmitters.	(Luo et al. 2018)
Detection of tetracycline	Tetracycline aptamer, and europium ions (Eu^{3+}) loaded onto nanosensors composed of MNPs and UCNPs	Tetracycline	On exertion of external magnetic field, the UCNPs and MNPs, conjugated with aptamer separate out and enable tetracycline detection.	Detection of antibiotics in food samples, scaling up of a simple, inexpensive and sensitive detection technique.	(Zhang et al. 2022)
Radiometric detection of pathogenic microbes	MNPs serve as core, silver shell function as SERS substrate, 4-mercaptobenzoic acid present as SERS standard and as an aptamer sequence for conjugation with *E. coli*	*Escherichia coli*	Magnetic enrichment of target cells, application of SERS to enable visualization of the microbes sensed.	Microbial detection in liquid food samples, lower cost and greater sensitivity in comparison with conventionally used strategies for operating SERS nanosensors.	(Weng et al. 2021)
Detection of micro-organisms using Diagnostic magnetic resonance (DMR) techniques	Handheld microfluidic device based on DMR employs proximity sensor to cross linked iron oxide -vancomycin particles that selectively bind to *S. aureus*	*Staphylococcus aureus*	MNPs bound to vancomycin act as sensors of the sequence d-alanyl-d-alanine on the surface of bacterial wall.	Non-invasive detection of micro-organisms based on DMR technique.	(Lee et al. 2008)

Table 1 contd. ...

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Application of magnetic nanosensors	Composition of nanosensors	Biomolecule detected	Brief overview of sensing principle	Future perspectives and scope for application	References
Quaternized chitosan (QCS) and graphene oxide (GO) based bactericidal MNPs	2D GO nanoagent with QCS coated on the surface of iron oxide nanoparticles	*S. aureus and E. coli*	Fe_3O_4@GO-QCS based nanoparticles show bactericidal activity. This activity is further enhanced by exposing to near infrared laser radiation.	Biocompatible nanocomposite for rapid sterilization.	(Shi et al. 2020)
Diagnostic kit for tuberculosis	Microfluidic device with miniaturized NMR readout for MNPs bound to Bacillus Calmette-Guérin (BCG) as a surrogate for *M. tuberculosis*	*Mycobacterium tuberculosis*	MNPs bind to the bacterial wall rendering them superparamagnetic. They shorten the T2 relaxation time of adjacent water molecules, which are assessed by NMR technique.	Microfluidic device for detection of tuberculosis and Mycobacteria.	(Lee et al. 2009)
DMR based diagnostic kit for cancer	DMR in combination with miniaturized NMR probe	*HER2/neu receptor* on *BT474* xenografted breast cancers	Sensor measures transverse relaxation rate of water molecules in the biological samples caused by target cells, which are labelled with MNPs (tumor cells (BT474) labeled with Mn-MNP-HER2) allowing detection within 15 min. The MNPs from FNA aspirates were also measured by ICP-AES.	Detection of different cancers in fine needle aspirations (FNA) using microfluidic devices.	(Lee et al. 2009)

Nucleotide detection using magnetic nanosensors	QD-C_{60}-based molecular beacon serving as a probe, conjugated with MNPs	Nucleic acid and DNA detection	Detection and capture of DNA sequences following introduction into the analyte. Application of magnetic field to improve sensitivity and accelerate fluorescence, to enable quantification.	Robust, reproducible detection method for biomolecules such as DNA sequences. Potential for developing fluorescent detection techniques without the addition of a label. Improvement of primary health outcomes.	(Liu et al. 2018)
Measurement of calcium and pharmacologic-al activities mediated by calcium in biological systems	Nanoparticles responsive to elemental calcium	Calcium ions	Following the introduction of calcium-responsive nanoparticles, usage of MRI to enable detection at low concentrations.	*In vivo* simulation of CNS responses to calcium ions, monitoring of neuronal signaling activities, potentials for enabling imaging of other deep tissues.	(Okada et al. 2018)
Detection of biomolecules such as streptavidin	Streptavidin detection using biotin conjugated to MNPs	Streptavidin	Bacterial magnetic particles using magnetic force microscopy (MFM) imaging.	Detection of immunoassay and DNA.	(Amemiya et al. 2005)
Estimation of glucose in biological samples	Co-precipitated nitrogen-doped graphene and MNPs nanocomposites	Detection of H_2O_2	Electrochemical detector.	Detection of peroxide and glucose.	(Zhang et al. 2016)
Detection of Procalcitonin protein	Magnetic bead-based immunoassay using both on-drop SPE-C and on-chip EMC-Au electrochemical detection	Procalcitonin protein	Magnetic bead-based immunoassay Bacterial pathogen surface plasmon resonance biosensor.	Disposable tools for clinical sepsis diagnosis.	(Molinero-Fernández et al. 2020)

Table 1 contd. ...

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Application of magnetic nanosensors	Composition of nanosensors	Biomolecule detected	Brief overview of sensing principle	Future perspectives and scope for application	References
Detection of prostate specific antigen (PSA) protease	Gold electrode with protein linkers tagged to MNPs, which renders the surface of electrode black	PSA protease	Colorimetric detection of PSA protease. Substrate releases black-coloured magnetic carrier complexes, exposing the gold colour sensor.	Washless cost-effective PoC devices for detection of various proteases.	(Suaifan et al. 2013)
Detection of glucose	Entrapped glucose oxidase (GOD) in chitosan composite doped with ferrocene monocarboxylic acid-modified magnetic core-shell Fe_3O_4@ SiO_2 nanoparticles (FMC-AFSNPs) attached to carbon paste electrode.	Glucose	Oxidase-based amperometric biosensors. Conjugate showed excellent efficiency of electron transfer between the GOD and the electrode for electrocatalysis of glucose.	Sensitive biosensor and bioelectronic devices for detection of glucose.	(Qiu et al. 2007)
Gene delivery for lung cancer	MNPs containing TRAIL gene and chitosan constructed by ionic gelation for magnetofection	TRAIL gene	Magnetic field causes internalization of MNPs tagged TRAIL gene in mouse melanoma cell line B16F10 *in vitro* induced TRAIL-protein expression.	Gene delivery for numerous disease conditions.	(Alvizo-Baez et al. 2016)
Delivery plasmid DNA encoding short hairpin RNA (shRNA) against Mcam (pDNA (anti-MCAM)) in B16F10 melanoma	MNP tagged pDNA	pDNA encoding shRNA against Mcam	Magnetic field causes internalization of intratumorally injected SPIONs-PAA-PEI-pDNA (magnetofection complexes) which leads to reduction in tumor volume.	Gene delivery for cancer.	(Prosen et al. 2016)

Treatment of cancers using Magnetic Hyperthermia (MHT)	Iron oxide nanoparticles are employed as intra-tumoral MHT agents under a patient-safe 100 kHz alternating magnetic field (AMF)	MNPs	100 kHz AMF causes rise in MNPs localized in tumour region by specific binding to receptor or by external magnetic field.	MHT therapy for treatment of prostrate and brain tumors.	(Gavilán, Avugadda et al. 2021)
Treatment of colon cancer using anticancer agent and MHT	Biocompatible niclosamide-loaded functionalized MNPs (NFMNPs)	Cancer cells	NFMNPs induced apoptosis in colon cancer cells about 7 times more compared to free niclosamide. Application of AMF causes MHT and slight increase in release of niclosamide.	Treatment of colon cancer using both MHT and chemotherapy.	(Ahmad et al. 2020)
Separation of cancer cells from blood using Ab-conjugated iron oxide nanoparticles	Iron oxide nanoparticles (30 nm) coated with antibodies (Ab) against human epithelial growth factor receptor 2	Breast cancer cells (SK-BR3)	Anti-HER2 or anti-HER2/neu antibodies on the surface of MNPs bind to the human epithelial growth factor receptor 2 which is overexpressed in breast cancer cells (SK-BR3) thereby allowing its detection and separation.	Capture and detection of breast cancer cells in blood.	(Xu et al. 2011)
Treatment of iron deficiency anemia	Iron oxide MNPs loaded liposomes	Iron	Iron oxide nanoparticles (10-100 nm) loaded in liposomes escape the RES and show enhanced blood circulation time in Wistar rats.	Superior treatment as compared to $FeSO_4$ in iron deficiency anemia.	(Fathy et al. 2019)

Table 1 contd. ...

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Application of magnetic nanosensors	Composition of nanosensors	Biomolecule detected	Brief overview of sensing principle	Future perspectives and scope for application	References
Biocompatible MNPs for purification of blood by non-specific removal of pathogenic bacteria	Imidazolium (thiol-terminated IBIL, 1-(12-(mercaptododecyl)-3-methylimidazolium bromide (MDMIBr)-based ionic liquid was immobilized in polydopamine coated Fe_3O_4 nanoparticles	*S. aureus*, *E. coli*, *P. aeruginosa* and methicillin resistant *S. aureus* and bacterial endotoxins	Positively charged imidazolium based ionic liquid on MNPs specifically bind to negatively charged pathogenic bacteria and endotoxins which are separated from the extracorporeal blood using external magnet.	Treatment of blood prior to sepsis.	(Shi et al. 2020)
MNPs for removal of arsenic from blood	MNPs coated with oleic acid containing cetyl trimethyl ammonium bromide (CTAB) and bovine serum albumin (BSA)	Arsenic	CTAB and BSA on the surface of MNPs enhance surface diffusion of arsenic, which facilitates its removal when an external field is applied.	Magnetic nano capture agent for heavy metals.	(Guo et al. 2019)
Iron oxide-based contrast agent for intraoperative visualization of parathyroid gland	Iron oxide nanoparticles (10 nm size)	Thyroid gland	Intense colored iron-oxide nanoparticles diffuse easily in the thyroid gland but cannot diffuse in tissue dense parathyroid gland, thereby allowing surgeons easy visualization during the operative procedure.	Effective and biodegradable contrast agent for differentiating between thyroid gland and parathyroid gland for surgeons during operative procedures.	(Zheng et al. 2022)

such as magnetite and maghemite, the magnetic moments are anti-parallel. However, their magnitude is unequal, and they do not cancel each other and possess a magnetic moment. Both antiferromagnetic substances and ferrimagnetic materials behave like ferromagnetic substances in the presence of an applied magnetic field. The choice of material for biosensing application generally depends on intended application and nature of the transducer element. Ferromagnetic or paramagnetic materials are most abundantly used for the preparation of MNPs (Issa et al. 2013).

It is reported that the substitution of divalent metal ions such as cobalt, magnesium, manganese, nickel and zinc into ferrite NPs significantly affects their magnetic properties. The magnetic moment of iron oxide MNPs was found to be enhanced when doped with metal ions such as manganese, cobalt and nickel (Sangsuriyonk et al. 2022). Ferrite materials using magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are commonly used in biosensing applications.

Size of the Particles

As there is a decrease in particle size from micrometre-to-nanometre scale, the percentage of atoms located on the surface increases with the increase in surface-to-volume ratio. This affects the coercivity field (H_C) and Néel (T_N) temperatures of MNPs (Kerroum et al. 2020). Magnetic domains are regions in ferromagnetic substances within which they exchange energy, dipolar energy and magnetocrystalline energy balance and align the whole region in one direction with a net magnetization. It is observed that MNPs below the size of 100 nm cannot exist as domains and are hence referred to as single domain particles (Issa et al. 2013). The properties of magnetic particles are related to their domain size rather than their particle size. In single domain particles, the spins are all aligned unidirectional and uniformly magnetized, leading to large coercivity (Obaidat et al. 2015). The magnetization in single domain NPs is reversed by spin rotation rather than motion through domain walls. The MNPs show superparamagnetic behaviour in which their magnetic moments fluctuate around the axis of magnetization (Issa et al. 2013).

The transition from single domain to multidomain with the change in particle size can be measured by coercivity field (H_C). Li and researchers reported that in the case of Fe_3O_4 NPs, a particle size below 20 nm was necessary to exhibit supraparamagnetic properties. For Fe_3O_4 NPs the critical size required to exhibit multidomain structure was 76 nm for a cube and 128 nm for a sphere (Li et al. 2017). On similar lines, Zhang and co-workers prepared $Ni_{0.5}Zn_{0.5}Fe_2O_4$ MNPs by sol-gel method that showed supraparamagnetic properties below 30 nm, whereas MNPs of higher size exhibited ferrimagnetic properties at room temperature (Zhang et al. 2013).

Surface Effects

Since MNPs have a majority of their atoms present on the surface, they are affected by numerous factors and their surface environment, which include vacant orbitals of atoms, uncompensated spins, surface strain, atomic coordination, lattice disorders, lead to uncompensated spins responsible for surface magnetization (Obaidat et al. 2017, Papaefthymiou 2004). Because of this, the particles exhibit ferromagnetism. Total magnetization of MNPs is due to two components, i.e., the surface effects and core effects. In ferromagnetic NPs, the surface often oxidizes to form metal oxides and forms antiferromagnetic shell around ferromagnetic core. This causes interactions between core and shell referred to as exchange coupling, which provides an additional magnetic coupling and helps in aligning ferromagnetic spin in certain directions (Issa et al. 2013).

Ortega and colleagues studied the effect of alkyl substitution on magnetic properties of Ni-NiO NPs. Different primary alkylamines such as octylamine, dodecylamine, tetradecylamine, hexadecylamine or octadecylamine were used as stabilizers (with metal: stabilizer in 1:10 ratio). They found that the surface composition of NPs was a combination of NiO and NiOOH. Best stabilizing effects were observed with tetradecylamine as stabilizer with 57.2% of Ni in metallic state. The particle size reduced with the size of primary amine ranging from 20 to 8 nm (Guerrero-Ortega et al. 2023). In conclusion, it was observed that the Ni metallic state composition and its particle size were the deciding factors for saturation magnetization.

Temperature

The temperature that a magnet is exposed to influences its pulling force, and an inverse relationship between the two parameters exists. Thus, it is observed that when a magnet is heated, its pulling force decreases. This may be attributed to a change in the flux density of the magnetic material with a rise in temperature (Shi and Weaver 2019). An increase in temperature results in an increase in atomic movements and randomness in the magnet, thereby decreasing the net magnetic field. Beyond a temperature, referred to as Curie temperature (named after Pierre Curie), certain materials lose their permanent magnetic properties (i.e., ferromagnetic substances change to paramagnetic). Neel temperature (named after Louis Neel) is the temperature beyond which certain antiferromagnetic substances become paramagnetic (Issa et al. 2013).

Planar Hall effect (PHE) sensors based on magnetorelaxometry are often utilized in biosensing, as they are small and can be easily integrated on chips. Temperature affects the Brownian relaxation of magnetic particles in such sensors (Alexandrov and Zhuravlev 2021). Thus, MNPs can be

applied to increase temperature in biological systems, often referred to as magnetic particle hyperthermia (MHT). The temperature of MNPs of defined size and geometric configuration can be controlled by placing it in an alternating magnetic field or applying an alternating current of defined strength. Depending on the specific absorption rate, it absorbs energy from the field and converts it into heat, leading to hyperthermia at the localized tissue (De La Encarnación et al. 2022). Gavilán and co-workers reported that anisometric MNPs give the best hyperthermic response to alternating current. Increase in H_{max} (magnetic field) led to an increase in specific absorption rate in materials with large shape anisotropy (Gavilán et al. 2021). Thus, modulation of temperature may be suitably undertaken as it has a direct bearing on magnetic properties.

Method of Preparation

Several steps are involved in the fabrication of magnetic nanosensors. The choice of each of these steps has a significant effect on the final properties of the sensor. The physical properties such as shape, size and magnetic properties of the MNPs are governed by their method of synthesis. Different physical and chemical methods have been reported for the synthesis of MNPs. These include hydrothermal, thermal, sol-gel, co-precipitation, to name a few (Tufani et al. 2021). MNPs have also been synthesized using different techniques in microfluidic devices (Frenz et al. 2008, Kritika and Roy 2022).

Their size and shape can also be modified by the use of surfactants. Sanksuriyonk and co-workers studied the effect of different surfactants, such as tween 80, cetyltrimethylammonium bromide, and sodium dodecyl sulphate on the preparation of $CoFe_2O_4$ MNPs. The resultant MNPs were of sizes 21, 20 and 16 nm, respectively as compared to those prepared without surfactant having a size of 42 nm (Sangsuriyonk et al. 2022). The MNPs can be designed to a defined size to fit their application. For imaging and delivery purposes, the particles are required to be smaller than 100 nm to ensure endocytosis into the target cells. However, the smaller size also leads to weaker signals, therefore in certain applications, particle sizes greater than 100 nm are desired. The magnetic particles can be functionalized using suitable biopolymers to make them biocompatible and to add linker elements for bioconjugation. The large bulky ligands stabilize the particles and prevent agglomeration due to electrostatic repulsion. The particles are then coated by gold, silver or silica to prevent oxidation of the core MNPs (Chen et al. 2017).

Silver-coated MNPs of iron oxide have been used for immunosensor application (Ngobili and Daniele 2016). The thickness of silica coating affects the magnetic properties of MNPs (De Mendonça et al. 2019). Silica coating (SiO_2) on MNPs also prevents agglomeration (Madhavi et al. 2022).

Spinel ferrites, MFe_2O_4, where M = Cu, Co, Ni, Mg, Mn, CoPt, FePt, and composites like FePt-Ag, Fe_3O_4-Ag, Fe_3O_4-Au, CdS-FePt, etc., have been prepared by sol-gel, co-precipitation, hydrothermal, high temperature decomposition, aerosol-vapour phase, flow injection, electrochemical process, oxidation, electron beam lithography methods, ball milling and microbial procedures (Alfareed et al. 2022).

MNPs with enhanced magnetic properties for biosensing application with *in vivo* detectability by MRI have been prepared by enhancing the R2 relaxivity, by increasing the saturation magnetization per mole of metal and particle diameter. This may be attributed to the fact that R2 is proportional to M^2d^2. Manganese doped metal oxide NPs have been reported to possess high Ms and R2s and is applied for a highly sensitive detection (2 cells/μL) with miniature relaxometer (Koh and Josephson, 2009).

Type of Detector Used

Several magnetic detection techniques are used for magnetic signal detection in MNPs. These include nuclear magnetic resonance (NMR) sensors, superconducting quantum interference devices (SQUIDs), spintronic sensors based on giant magnetoresistance (GMR), tunnel magnetoresistance (TMR), and PHE, atomic magnetometer (AM) based sensors, fluxgate sensors, Faraday induction coil sensors, diamond magnetometers, and domain wall-based sensors, etc. (Chen et al. 2017). The choice of the sensor depends on the size of MNPs. Their method of detection can be classified as surface- or volumetric-based. Volumetric sensors, for instance, PHE- and NMR-based sensors, can quantify easily and do not require elaborate sample preparation steps (Shao et al. 2010). Surface-based sensors, such as GMR, TMR, offer higher sensitivity and lower detection limit as the sensing element is placed very close to MNPs (Su et al. 2019). The choice of the detection method is governed by the parameters such as sample size, magnetic property, intended application, presence of interfering substances, sensitivity, specificity to name a few (Koh and Josephson 2009). Figure 1 offers an insight into major factors governing the performance of nanosensors.

Nanotechnology based Modification of Magnetic Sensors

Magnetic biosensors comprise two main elements, the recognition elements (enzymes, antibodies or nucleic acid) and transduction devices (Naresh and Lee 2021). The use of nanotechnology in biosensors has made their miniaturization possible, and has enabled selective transportation into specific tissues and cells. Nanomaterials exhibit varied properties once they are scaled to nanosize, which can be applied to enhance their

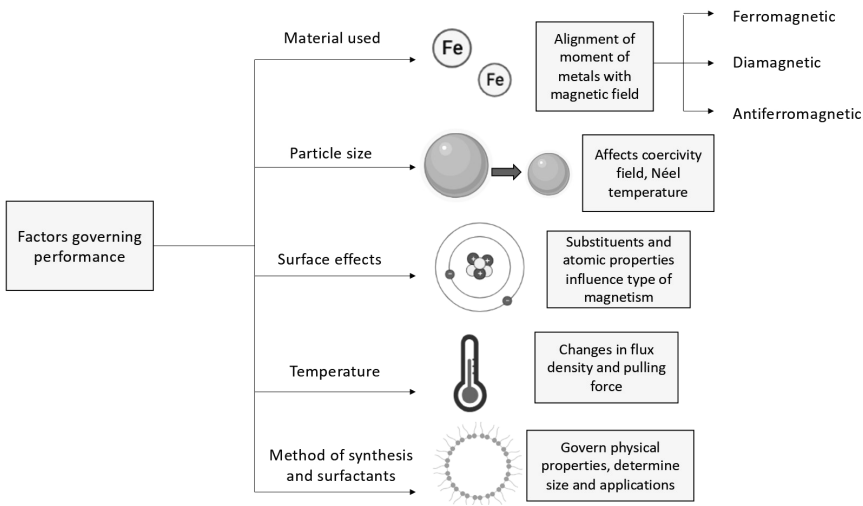

Fig. 1. Insight into major factors governing the performance of nanosensors.

sensitivity and specificity (Huang et al. 2021). Nanomaterials with their high surface-to-volume ratio, enhanced mechanical strength, mechanical activity, catalytic properties and diffusibility have proven to provide biosensors with attributes that were previously thought to be impossible (Malhotra and Ali 2018). The recent technologies such as microfluidics, microelectromechanical systems (MEMS) allow for precise nanofabrication with enhanced sensitivity, stability and versatility. The parts of biosensors that have been modified using nanotechnology are bioreceptors and transducers (Tovar-Lopez 2023, Zhang et al. 2009).

Nanotechnology Based Bioreceptors

Bioreceptors use different biomolecules such as proteins (enzyme, antibody, etc.), nucleic acids, cells, tissues, or the whole organism whose biochemical mechanism is well understood and can be applied for signal detection without any interference from surrounding molecules. With advancements in technology, molecular imprinted polymers also now serve as bio-receptors providing a binding site for biomarkers. These biomolecules and polymers aid in selective detection at the sensor thereby providing an accurate estimate of the biomarkers and biological processes (Akgönüllü et al. 2023, Shinde et al. 2012).

MNPs or magnetic beads made from materials such as iron, cobalt, nickel and manganese are used as labels and conjugated with bioreceptors. The conjugation of magnetic particles to bioreceptors offers numerous advantages. As most biological molecules are non-magnetic, these signals can be accurately estimated *in vitro* and *in vivo* without considerable background noise. The conjugated magnetic particles can easily be

separated from the complex matrices by applying a magnetic field, thereby minimizing tedious steps of filtration and centrifugation (Kim et al. 2020). The conjugation facilitates ease in purification, enhanced sensitivity, selectivity, and easy amplification of signals. MNPs are functionalized by two approaches, first, molecular functionalization which employs sequential growth or coating with polymers for binding bio-functional molecules to allow these to be 'tagged', and second, interaction with other materials such as metallic NPs or coatings which offer distinct surfaces for imaging (Chinese Academy of Sciences et al. 2015, Materón et al. 2021). The immobilization of the labelled biomolecules on the surface of the sensors is generally done by covalent linkages or by supramolecular associations. The covalent linkages involve a covalent bond formation between the biomolecule and the sensor and is chiefly done by formation of amide linkage, cross-linking reactions, coupling reactions or by click chemistry approach. The covalent bond provides strong anchorage, stability, and reproducibility to the surface. However due care should be taken that the binding domain of biomolecules should remain unhindered for the detection of the analyte. Immobilization by non-covalent bond formation involves supramolecular or coordinate bond formation. Techniques such as physical entrapment in polymer, electrostatic attraction, van der Waal's interactions, etc., are used to bind biomolecules to the sensor (Liébana and Drago 2016, Liu et al. 2016). In physical entrapment methods, the bio-molecules or bioreceptors are entrapped into a porous network of polymer. Pore sizes can be controlled by the density and degree of cross-linking in polymerization reaction. A smaller pore size of the polymer helps in retaining the bioreceptors stably on the surface of the sensor. Examples of polymers used for the purpose of entrapment include polyacrylamide, agar, gelatine, carrageenan and cellulose triacetate. Another non-covalent technique used is the encapsulation of bioreceptor molecules in a semipermeable membrane. The pore size of the membrane prevents bioreceptor molecules from diffusing out and hence they remain confined inside the capsule. The pervious nature of the membrane allows free diffusion of analyte molecules (Malhotra and Ali 2018).

Nanomaterials can also be equipped for biomolecule immobilization by functionalization at the time of their synthesis or by coating them with functionalized moieties, post their synthesis. Coating has, in certain cases, been observed to aid in providing biocompatibility without affecting functional and binding properties (Holzinger et al. 2014). One common method of immobilization is the utilization of a streptavidin-biotin (Vit B7) complex. Streptavidin is a tetrameric protein obtained from *Streptomyces avidinii*. The streptavidin-biotin (Vit B7) complex is a very strong non-covalent complex found in nature. Biotin is immobilized on

the surface of materials such as silicon, nickel, etc., via thiol-maleimide using methods such as Michael addition method (Seto et al. 2013, Zhang et al. 2020). The complex is prepared by the addition of the biotinylated antibody or ligand to a cell and subsequent labelling with streptavidin coated magnetic beads. These cells are then attracted to the magnetic field and can easily be separated and immobilized. The ability of this complex to accommodate varied antibodies makes it a versatile bioreceptor for immunoassay. Another protein, avidin, is also used, but it has lesser binding affinity to biotin than streptavidin (Han and Wang 2010).

Covalent binding can be carried out on cross-linked iron oxide (CLIO) NPs made of monocrystalline iron oxide particles. They contain a mixture of magnetite (Fe_3O_4) and/or maghemite (γ Fe_2O_3). In comparison to magnetite, maghemite contains cation vacancies in its sub-lattice (Can et al. 2012). These particles are coated with dextran and functionalized by treatment with epichlorohydrin and ammonia, to generate amine functionalities on the surface for binding (Sun et al. 2006). Depending on the functional group desired on the surface, the amines are subsequently made to react with different reagents to generate carboxy, hydroxyl, anhydride, thiol groups for binding to biomolecules (Haun et al. 2010).

Nanotechnology Based Transducer

Transducers are components of biosensors responsible for converting the interactions into magnetic signals. The bioreceptor or biosensing element is connected to a transducer, which then relays the signal to the detector. MNPs are used as transducers based on different sensing mechanisms such as magneto-optical properties, magneto-resistance, changes in coil inductance and magnetic reed switches, which aid in selective detection (Yang and Zhang 2021). For certain molecules, especially affinity binding reactions, it is not possible for the receptors to detect the binding signals by transduction. Few examples include immune reaction (antigen-antibody complex) or DNA hybridization reaction. In this case, labelled bio-specific components such as modified antibody or a DNA strand with desired magnetic attributes must be added. Interaction with the target analyte must be able to produce changes in the magnetic properties of MNPs. These are then detected by coils, GMR devices, NMR, MRI, PHE devices, to name a few. The binding capacity and ability of MNPs to analyte molecules in biosensors can be altered by tuning its properties in applied magnetic field, thereby enhancing its sensitivity. Magnetic materials are conjugated to polymers, metals or carbon hybrid materials to bring about transduction of the signals. These utilize electrochemical, optical or piezoelectrical sensing systems (Feier et al. 2022, Kaushal et al. 2023).

Sensing Mechanisms used in Signal Transduction

Electrochemical

These sensing devices are based on electrochemical signals generated when an analyte interacts with a sensor. The electrochemical signals such as change in voltage, current or impedance are measured, which are then amplified by magnetic particles. Biomaterials are immobilized on the surface of the electrode as thin films and when the interaction with the analyte occurs, the electrochemical changes on the surface of the electrode are detected. The electrochemical sensors use MNPs as supports and/or labelling agents. MNPs have also been incorporated on Quantum Dots to enhance its sensitivity (Sun et al. 2023). Zhou and co-workers prepared a sandwich-type electrochemiluminescence immunosensor on glassy carbon electrode for detection of α-fetoprotein (AFP) based on enrichment with magnetic capture probes. The capture probe was prepared by immobilizing the antibody on Fe_3O_4-Au MNPs. After binding, they formed Fe_3O_4-Au-Ab-AFP complex, which could be easily separated from the sample via magnetic separation. The CdS-Au based quantum dots were coupled to second Ab (CdS-Au-Ab2), which was then allowed to react with first complex in a sandwich-type assay, which could easily be separated and produce electrochemical signals at fixed voltage. The immunosensor could detect trace level signals of this cancer biomarker with a sensitivity of 5 ng/mL and limit of detection (LoD) 0.2 pg/mL (Zhou et al. 2012).

Zamfir and researchers prepared a label-free gold electrode immunosensor based on functionalized MNPs for detection of ochratoxin A. They immobilized bovine serum albumin (BSA) on the surface of a gold electrode using glutaraldehyde-thiolamine linker. Ochratoxin A specific antibodies were attached to MNPs using carbodiimide chemistry and these were then immobilized on the gold electrode. Variation in impedance during ochratoxin A-antibody interaction was measured using Electron Impedance Spectroscopy. The sensor was able to linearly detect between concentrations of 1–50 ng/mL with LoD of 0.01 ng/mL (Zamfir et al. 2011).

Guo and colleagues developed a photo-electrochemical immunosensor harnessing MNPs for detection of SARS-CoV-2 nucleocapsid protein detection based on magnetic all solid-state Z-scheme heterojunction. The sensor was developed using FSTCA technique, which involved coating with composite layer of TiO_2, CdS, and Au (the combination of which is abbreviated as TCA) NPs on Fe_3O_4-SiO_2 (FS) surface. The objective of the FSTCA technique was to enhance the separation and purification of immune complex. It was also observed to inhibit the recombination of photogenerated e–/h+ (electron/hole) and promote light absorption providing enhanced photoelectric substrate signal. The response

generated by binding of SARS-CoV-2 nucleocapsid protein e–/h+ transfer was captured by ESR. This method was highly sensitive with a detection limit of 2.9 pg/mL (Guo et al. 2023).

Optical

Some commonly used optical properties in the detection of biomolecules include light scattering, refractivity, chemiluminescence, fluorescence and light interference (Roy 2022). MNPs are also coupled to optical sensors to enhance their sensitivity (Üzek et al. 2019). Coupling of optical sensing elements with MNPs in an effort to detect changes in fluorescence, chemiluminescence, surface plasmon resonance have been reported for biosensing applications. Wang and co-workers observed a 4-fold increase in sensitivity of detection for β-human chorionic gonadotropin (βhCG) when they used MNP-enhanced Grating Coupled-Surface Plasmon Biosensor (GC-SPB) as compared to conventional GC-SPB (Wang et al. 2011).

Zang and co-researchers prepared nanocomposite Fe_3O_4–Au nanorod (AuNR) that exhibited both optical and magnetic properties. The nanocomposite was utilised as a substrate for surface Plasmon Resonance (SPR) biosensor to detect goat IgM. The conjugation with MNPs was found to be beneficial for immobilization of Ab, enhancing the sensitivity of the biosensor, which exhibited a satisfactory response in the range of 0.15–40.00 μg/mL when compared to that without MNPs 1.25–40.00 μg/mL (Zhang et al. 2012).

Liang and colleagues developed core–shell Fe_3O_4@Au MNPs for SPR-based sandwich immunoassay for detection of α-fetoprotein (AFP). The method involved binding of AFP antibody (Ab1) on the surface of 3-mercapto-1-propanesulfonate/chitosan-ferrocene/Au-NP (MPS/CS-Fc/Au-NP) film. Following the binding of AFP to Ab1 complex, a secondary complex comprising of Fe_3O_4@Au–Ab_2 was applied as amplification reagent. A significant amplification aided in detection of trace levels of AFP in samples with a good correlation in the range of 1.0–200.0 ng/mL and LoD of 0.65 ng/mL (Liang et al. 2012).

Piezoelectric

This type of sensing technique involves either a quartz-crystal microbalance (QCM) or surface acoustic wave. The QCM utilizes a disc made of quartz crystal with metal electrodes located on each side of the disc. As the disc oscillates in the presence of an electric field, its resonant frequency is found to vary depending upon compounds that adsorb and desorb from the crystal surface. It was observed that the frequency decreased with the mass of the absorbed compounds. QCM is very sensitive to

mass change of even one nanogram and hence can be applied to sense binding of biomolecules on the surface of a sensor. However, its limitation as a nanobiosensor is that, as the size of the disc decreased there was an increment in the noise, which hampered the accurate determination of the analyte. Atmospheric humidity has also been found to interfere with measurements. Here, conjugation of MNPs to piezoelectric components can be advantageous, as MNPs exhibit piezoelectric properties that can capture and aid in accumulation of analytes on the surface of QCM and provide a matrix for loading labels (Rocha-Santos 2014)

Wan and co-workers developed a QCM-based biosensor for detection of *D. desulfotomaculum, a sulphate reducing bacterium. They used vancomycin,* a glycopeptide antibiotic that forms 5-point rigid H-bond with D-Ala-D-Ala domain in gram-positive bacteria. Vancomycin functionalized MNPs were prepared to selectively bind and isolate the microorganisms from a sample under applied external magnetic field. The agglomerated bacteria could be detected by the QCM sensor. Further amplification of the signals was achieved by applying an external magnetic field and magnetizing the bacteria-MNP conjugates on the surface of gold electrode (Wan et al. 2010).

Shen and colleagues also prepared QCM-based biosensors for detection of *E. coli* O157:H7. MNPs coated with polyclonal anti-*E. coli* O157:H7 antibody (target antibody) and biotin-IgG (beacon antibody) at an optimized ratio of 1:60, were placed in analyte solution to bind with bacteria. The streptavidin gold was added and allowed to conjugate with *E. coli* O157:H7. These complexes were then separated by magnetic plate. The particles were dried and the frequency shift of QCM was observed to detect the concentration of bacteria (Shen et al. 2011).

Magnetic

One of the recent techniques in this category includes Diagnostic Magnetic Resonance (DMR), which has now advanced with the development of highly sensitive miniaturized chip-based NMR systems (Shao et al. 2010). MNPs show supraparamagnetic properties producing a large dipole when subjected to external magnetic field. This local field gradient is responsible for creating in-homogeneity in the external applied magnetic field and disturbs the precession of nuclear spin in protons of the adjacent water molecule, which can be quantified by H^1-NMR or MRI techniques. Between the two values, T_1 (longitudinal spin lattice) and T_2 (transverse spin-spin), T_2 is generally used for biosensing applications as transverse relaxivity (r_2) is significantly higher for most of the MNPs, thus, very few MNPs are required (Shao et al. 2010). The DMR-based sensors employ affinity-based binding of MNPs to target cells/organelles/molecules and induce changes in proton relaxation in two modes. First mode includes tagging large structures such as cells/organelles and subsequent washing

to eliminate untagged moieties. In the second mode, a phenomenon called Magnetic Relaxation Switching (MRSw) is applied, wherein molecular targets are used to assemble MNPs into clusters, thereby affecting bulk relaxation rate (Lee et al. 2008). DMR-based sensors are capable of quantifying varied biomolecules such as human tumour cells, pathogens, DNA, mRNA, metabolites and drugs (Haun et al. 2010).

Grimm and colleagues developed a magnetic biosensor based on MRSw, which on annealing with the telomeric sequence TTAGGG repeats, was able to switch their magnetic state and could be easily detected by magnetic readers. As the levels of telomerase are found to be elevated in cancerous cells, these detectors could find their application in *in-vivo* cancer sensing (Grimm et al. 2004). Similarly, Sun and co-workers developed magnetic nanoswitches based on protein binding. They developed a magnetic nanosensor by binding MNPs to glucose, folic acid and hemagglutinin peptide to detect proteins such as Concanavalin A, antibody to folic acid and antibody to hemagglutinin peptide, respectively. The functionalization of MNPs with glucose, folic acid and hemagglutinin peptide was done with CLIO using suitable linker molecules. The lowering of T_2 relaxation time after addition of proteins could be detected by NMR or MRI techniques (Sun et al. 2006).

Giant magnetoresistance-based (GMR) sensors work on the principle that when the external magnetic field and ferromagnetic film are separated by a thin non-magnetic layer, its orientation of magnetization strongly influences resistance of the system. The strength of the current change determines the number of labelled particles bound to the non-magnetic bioreceptors coated layer. The sensitivity of these detectors depends upon the distance between the labelled particles and the sensitive surface. The sensitivity of GMR is inversely proportional to the distance between the labelled particles and the sensor and hence, it is desired that the layer of biomolecules coating the sensor should be as thin as possible. For GMR-based sensors it is also desirable to use magnetic particles with high magnetic moments such as FeCo alloys (Ennen and Hütten 2017, Hossain et al. 2022).

Applications of Magnetic Nanosensors in Diagnosis

Nanosized magnetic biosensors have also been developed for detecting biomarkers in cancer, stem cells, pathogens (bacteria and virus), certain drugs and toxic-metal ions. Nanosized magnetic particles show superparamagnetic properties and result in rapid response and relaxation timing, enhancing the sensitivity of biosensors. MNPs are relatively stable, not prone to photobleaching and readily traceable due to their magnetic properties. MNPs are employed in detection by assessing the change in the magnetic field due to the interaction with the analyte or they can be used

as a complementary approach to enhance their separation and sensitivity. MNPs allow the detection of different biomarkers *in vitro* and *in vivo*. MNPs have been used for cancer diagnosis and imaging. Numerous mechanisms have been explored to utilize MNPs for the detection of biomarkers.

Selective protease from microorganisms and certain cells have been used by researchers to develop point-of-care (PoC) detection devices for various organisms and disease conditions. Proteases are proteolytic enzymes that are involved in cellular processes and have been linked with disease conditions such as cancer, inflammation, vascular diseases and Alzheimer's. MNP-tagged protein linkers are connected to gold electrode surfaces rendering the surface black. The coated surface when exposed to specific proteases causes selective cleavage of the linker protein, releasing the MNP coat and making the gold surface underneath visible. The amount of MNPs dislodged can be quantified by different methods (Rodriguez-Rios et al. 2022). Eissa and Zourob developed a PoC device for determination of *Staphylococcus aureus* based on its protease enzyme using colorimetric and electrochemical detection. The PoC device utilized magnetic nanospheres coated peptide sequence that were immobilized on gold screen printed electrodes, rendering the surface black. When *S. aureus* protease cleaved the protein linker, it released the MNPs, and made the gold surface underneath visible, which was detected using square wave voltametric signals with ferro/ferricyanide redox couple (Eissa and Zourob 2020). Wignarajah and colleagues used this principle to design colorimetric assay for detection of Human Neutrophil Elastase (HNE) and Cathepsin-G, which are biomarkers for periodontitis. In this method, the probe contained immobilized specific protease covalently bound to magnetic beads from one end and to the gold sensor surface on the other end. When these protease probes were digested by the HNE and Cathepsin-G, the magnetic particles were set free from the gold surface, and the golden colour of the surface was quantified by colorimetric assay (Wignarajah et al. 2015).

Affinity-based sensors work on the principle of strong and selective binding of a specific biomolecule to receptors, antibodies, oligonucleotides, to name a few. Affinity-based sensors are used for immunoassays. MNPs labelled biomarkers (antibodies) are generally involved in sandwich-type assay. The number of biomolecules bound can be quantified using different methods such as change in magnetic field, SPR, electrical conductance, piezo effects, etc. Giant magnet resistive (GMR)-based immunosensors involving MNPs have been used for cancer diagnosis and imaging. SPR-based sensors have been employed for immunoassay. In this type of assay, magnetic core particles are coated with polymers to which antibodies with affinity to specific biomarkers are immobilized. MNPs, when bound to SPR-based sensors, enhance their response by increasing the mass on the surface due to binding. SPR-based sensors can be reused and

are thus sustainable (Wang et al. 2010). Saylan and coworkers prepared MNP-coated surface-modified plasmonic biosensors for the detection of α-interferon in plasma samples. This metal affinity based coupled biosensor allowed for real time monitoring in plasma samples with a very high correlation coefficient (0.99) and LoD of 41 IU/mL (Saylan et al. 2022). Table 1 summarizes various diagnostic applications of MNPs.

Applications of MNPs as Theranostics

Theranostic MNPs, which are able to perform both diagnostic as well as delivery of therapeutic agents in a single bolus, have been developed. MNPs allow surface modification and binding of drug molecules. They have a longer residence time, are easily available and cost-effective, which makes them suitable candidates for targeted drug delivery. These particles are often coated with biocompatible polymers to offer inertness in biological systems. Magnetic fluid hyperthermia can be generated in MNPs by application of alternative magnetic field to reach temperatures ranging from 40–45°C. Rahimi and co-researchers prepared dendritic chitosan grafted mPEG coated MNPs for delivery of anticancer agents like doxorubicin and methotrexate. The dendritic matrix allowed 95.95 and 67.91% for encapsulation of doxorubicin and methotrexate, respectively which also allowed pH-based controlled release of drug in the tumour microenvironment (Rahimi et al. 2017). Chen and colleagues prepared a reducible co-polymer of polyamidoamine with polyethylene glycol (PEG)/dodecyl amine graft self-assembled with supraparamagnetic iron oxide NPs (SPIONs) intercalated with oleic acid capped on surface of magnetite nanocrystals. Doxorubicin was entrapped in the intercalating area and its delivery was traced using an MRI detector (Chen et al. 2014). Shen and coworkers prepared MNPs containing doxorubicin and indocyanine green for chemotherapy of glioma. They coated hydrophobic SPIONs with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG 2000) and doxorubicin using thin film hydration method and subsequently loaded them with indocyanine green into the phospholipid layer. This allowed delivery of drug and simultaneous determination using fluorescence and MRI-based detectors (Shen C et al. 2018). Several other reports on utilization of MNPs for delivery of doxorubicin have been published as summarized in Table 1. Avedian and colleagues developed a pH-sensitive magnetic mesoporous silica NP-based carrier for anticancer drug erlotinib. The pH-sensitive shell was prepared by conjugating poly(ethyleneimine) with folic acid. Poly(ethyleneimine) acts as a pH-responsive polymer, whereas folic acid aids in binding to the folate receptor located on cancerous cells (Avedian et al. 2018). Fathi and coworkers prepared methotrexate conjugated thermo- and pH-responsive MNPs for targeted delivery of

erlotinib in ovarian cancer. They used *N*-isopropylacrylamide (NIPAAm) as thermoresponsive polymer and itaconic acid as pH-responsive polymer and grafted it on chitosan. An MNP-based ferrofluid was prepared via formation of inclusion complex between carboxylic acid of chitosan copolymer and MNPs. Methotrexate was conjugated to amino groups to offer specific binding to folate receptors on cancer cells (Fathi et al. 2020). Han and coresearchers prepared two-step delivery of gemcitabine-loaded MNPs for therapy of pancreatic cancers. In this method they used metformin to disrupt dense stroma and downregulate the expression of fibrogenic cytokine TGF-β, which is involved in the suppression of pancreatic stellate cells. Subsequently gemcitabine and pH (low) insertion peptide (pHLIP) modified MNPs were administered and traced with MRI detectors (Han et al. 2020).

Gene delivery using MNPs is also possible using a technique called magnetofection. In this technique, MNP-tagged DNA is incorporated into adherent cells by applying magnetic field placed below the cell. The MNP-tagged DNA is thus physically internalized by endocytosis or pinocytosis. This method facilitates internalization within 10–15 min, which is faster than many other transfection methods (Majidi et al. 2015). MNP-based gene delivery allows to target the genes responsible for the disease condition such as cancer, CVS disorders and CNS as reported in human xenograft tumor models as well as internal organs and CNS (Li et al. 2012).

MNPs can specifically be bound to cancer cells, bacterial cells and certain proteins, which can then be separated from the blood by application of magnetic field (Shi et al. 2020, Xu et al. 2011). The clinical applications MNPs as theranostics have been depicted in Figure 2.

Bench-Side to Commercialization

Functionalized MNP-based biosensors have been used to achieve targeted drug delivery and highly sensitive detection. Owing to their high surface area (> 100 m^2/g) the NPs can carry a huge payload of drug molecules on their surfaces at the same time. As a result of their magnetic properties, they can be easily traced in tissues. Although the *in vivo* therapeutic applications of these techniques are still awaiting regulatory approvals, such techniques offer several advantages over the conventional detection and drug delivery techniques. Magnetic nanosensors have been carefully engineered to improve their sensitivity in biological systems by enhancing their supraparamagnetic properties. A surface modification of these is done to make them biocompatible and to facilitate targeting. MNPs are commonly functionalized with Ab for specifically targeting cancer cells. They are also tuned to cause magnetic hyperthermia to kill cancerous cells. An external magnetic field can be applied to enrich the tissue and retain the particles

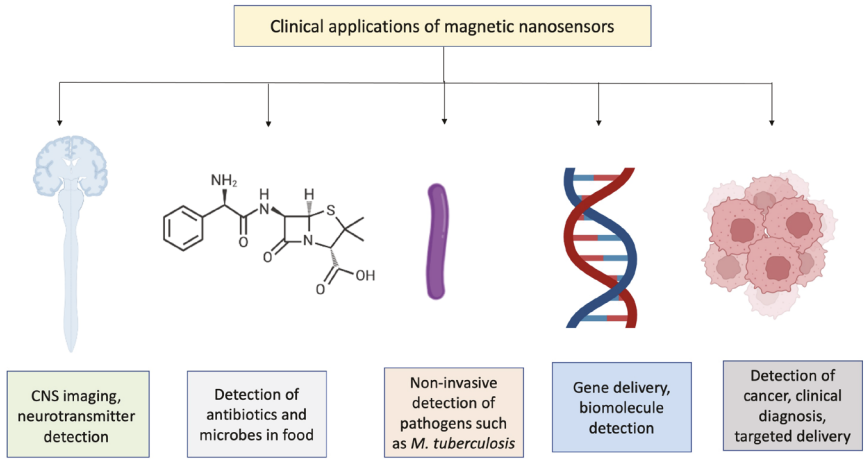
Clinical applications of magnetic nanosensors
CNS imaging, neurotransmitter detection
Detection of antibiotics and microbes in food
Non-invasive detection of pathogens such as M. tuberculosis
Gene delivery, biomolecule detection
Detection of cancer, clinical diagnosis, targeted delivery

Fig. 2. Overview of clinical applications of magnetic nanosensors.

in a selected area, such as tumours. Owing to their nanosized diameter (<100 nm), MNPs are reported to show less enhanced permeation retention (EPR) in humans, as compared to rodent models. MNPs, once inside the biological environment, form a nanoparticle-protein corona by adsorbing proteins such as immunoglobulins onto their surface (Kalubowilage et al. 2019). Depending upon the affinity of protein, they can form hard or soft corona. Low affinity proteins form a soft corona whereas high affinity proteins are irreversibly adsorbed and form a hard corona. As the residence time of MNPs in the biological systems increases, the low affinity proteins of soft corona get replaced by high affinity proteins to form hard corona (Huang et al. 2021). This coat then sterically blocks the active sites of MNPs controlling diffusion, targeting, uptake, clearance of particles and delivery of the drug from its surface (Casals and Puntes 2012). MNPs are internalized by endocytosis and once they reach the cytoplasm, they release drug molecules and start to degrade in the cell. Additional requirement for MNP-based sensors is that they should be cleared from the body once their function is over. As accumulation of these in tissues may lead to toxicity, at the same time ensure adequate residence time for efficacy. For MNPs > 10 nm, the elimination largely depends upon their uptake by reticuloendothelial system (Nam et al. 2013). Several efforts are being implemented to make biosensors more compatible and less toxic. MNPs for biological applications such as FerroMag™ with PEG shell, 10 nm size and median lethal dose, MTD50 > 1 Fe/kg in mice are commercially available (Wu et al. 2021).

Pottler and co-workers studied the genotoxicity of supraparamagnetic iron oxides in human granulosa cells (HLG-5). In this study, they exposed

and examined the effect of supraparamagnetic iron oxide particles coated with lauric acid, corona of BSA and dextran on reproductive cells such as HLG-5, which are vital for ovarian function and fertility. They reported no genotoxic effect based on micronuclei testing and γH2A.X biomarker analysis (Pöttler et al. 2015).

Herrmann and colleagues carried out the risk evaluation studies of platinum spiked carbon coated iron carbide NP in mice. They reported platinum spiked iron carbide NPs coated or functionalized with PEG and IgG when administered in mice were principally localized in lung and liver (reticuloendothelial organs), 1 week following administration. Analysis over a one-year period revealed that the particles were still located in reticuloendothelial organs without any inflammation, fibrosis, necrosis or carcinogenesis. These studies hold promise for future biomedical application (Herrmann et al. 2016).

Schumacher and co-researchers developed a method for quantitative separation of polyethylene glycol coated MNPs, such as magnetite (Fe_3O_4) and cementite (Fe_3C) from both static and flowing conditions. This method may aid in the removal and attenuation of toxicity of MNPs after their application in theranostics (Schumacher et al. 2013). Commercial kits for delivering genetic material via magnetofection are now available. The application of a magnetic field enhances the contact of tagged gene with cells and facilitates internalization. This technology makes it possible to have high transfection rate with very low toxicity to host cells (Sizikov et al. 2021).

MNP-based biosensors have been immobilized on numerous lab-on-chip devices for the detection of biomarkers in diseases such as cancer, utilizing giant magnetoresistance sensors as detectors (Chuc et al. 2021). Microfluidic devices and lateral flow assays utilizing magnetic and hydrodynamic properties of supraparamagnetic NPs have been developed for continuous separation and detection of biomolecules such as antigens. Such technologies make it possible for MNPs to react inside minute liquid channels located inside the microchips. Tunnel magnetoresistance sensors (TMRs) are a type of magnetorestive sensors, which use extremely thin layer of non-magnetic material sandwiched between two ferromagnetic layers, and have a higher sensitivity than GMR sensors (Ren et al. 2020). The integration of TMR technology in microchips has made it possible to accurately quantify the number of MNPs in biological systems. Microfluidic-based devices have been used to quantify the biomarker molecules in blood, urine, plasma and serum samples *in vitro* for detection of disease. These devices are able to simultaneously quantify multiple analytes using magnetic particle plugs, which are immobilized within the microfluidic channels (Murzin et al. 2020). Bronzeau and co-workers developed a microfluidic device consisting of three plugs of glycine,

streptavidin, and protein A for detection of various antibodies (Bronzeau and Pamme 2008).

Conclusion

Over the last few decades, there has been a surge in interest with respect to nanomedicine, in an effort to improve clinical outcomes. This, in turn, has prompted numerous research efforts in the domain of nanosensors, which offer platforms for targeted delivery, offering advantages such as reduced dosing, site-specific interventions and lower side-effects. This chapter aimed to offer an overview of the advances made in research, offering a mix of synthetic approaches and a focus on physicochemical properties of these agents, as well as clinical applications, to bridge the gap between the bench and bedside. Citing recent studies, the authors have tried to present an overview of research relevant to the pharmaceutical and clinical domain, as well as certain lacunae that must be addressed, moving forward.

As research continues, newer applications continue to emerge. A noteworthy advancement has been the advent of MNPs located within the microchannels. Technologies such as lithography, electrospinning and 3D printing have simplified the production of such sensors (Ennen and Hütten 2017), opening up avenues for clinical translation and subsequent scaling-up of usage.

However, a major drawback is that the application of these devices *in vivo* still lacks regulatory support, and more evaluations on their safety need to be carried out (Kalubowilage et al. 2019). In addition to this, there is a pressing need to factor the possible risks and carefully assess the effects of nanomaterials in biological systems, entailing the need for focused clinical efforts. Gaining a better understanding of the safety and toxicity profile of these systems would pave the way for incorporating a greater diversity of therapeutic agents, as well as exploring opportunities such as personalized medicine, to reduce resistance and enhance the quality of life of patients.

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5

Unveiling the Dynamic Realm of Ultrasound Nanosensors

Exploring its Advancements and Promising Prospects

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Introduction

The human body acts as a complex supramolecular system, modulated by different bio-dynamic processes (Rong et al. 2019). The variations in bio-molecule concentrations and physiological processes offer valuable information, which helps to design therapeutic strategies to address dysregulations in predominant mechanisms at the molecular level (Kim et al. 2017, Rong et al. 2019). A sensor is a device capable of sensing changes and translating them into tangible and recordable messages in the physical environment (Mousavi et al. 2018). Such a device generally acquires a physical value and transforms it into the desired signal for processing (Polat et al. 2022). Sensors are vital tools used in monitoring biofunctions and biomolecular changes. They encrypt important information with

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respect to bodily functions. Sensor-based technologies enable clinicians to make informed decisions and in turn, offer benefits to patients as well (Gashgari et al. 2016).

Medical imaging and diagnostics are two key pillars of personalized medicine and are beneficial for understanding the onset and progression of disease conditions (Cash et al. 2015b). The past few decades have witnessed enormous improvements in non-invasive medical imaging (Lim et al. 2020). Unlike several other diagnostic imaging technologies, ultrasound has undergone technological improvements that have greatly improved sensitivity, permitting the harnessing of 3D knowledge and enabling the measurement of complex physiological processes such as blood supply and tissue motion (Kaufmann and Lindner 2007).

Ultrasound is conveniently used as a medical imaging and diagnostic technique owing to its mobility, non-invasiveness and tuneable tissue penetration (Chen et al. 2017, Sigrist et al. 2017, Walker et al. 2020). Ultrasound energy, a type of mechanical energy from sound waves produces an impact on cell function and has shown to be beneficial for drug delivery. A transducer is a crucial component of ultrasound imaging. The construction of this component typically comprises piezoelectric crystals that convert electrical energy into mechanical vibrations (sound waves) and vice versa. When an electrical voltage is applied, these crystals vibrate, producing ultrasound waves. These ultrasound waves are transmitted at varying frequencies and the transducer receives the echoes (or signals) that bounce back from internal structures. The reflections of acoustic waves are sensed and generate the image (Aldrich 2007).

Therefore, the capacity to use ultrasound energy of a specific intensity enables a range of clinical applications (Tharkar et al. 2019). Additionally, ultrasound-mediated drug delivery has been facilitated due to the enhanced permeability of cell membrane, induced by sonoporation (Tu and Yu 2022). The acoustic cavitation increases the permeability of plasma membrane; nevertheless, the integrity of the membrane is regained within few seconds. Thus, ultrasound therapies have emerged over the last decade with promising treatment modalities for cancer and other medical conditions (Zhou et al. 2020). However, there is an immense need to further develop novel approaches and technologies using ultrasound for *in vivo* imaging and for monitoring physiologically important analytes (Zhang et al. 2022).

Ultrasound contrast agents permit clinical applications such as blood pool enhancement, characterization of liver lesions or perfusion imaging, to name a few (Spann and Fetzer 2021). The Food and Drug Administration (FDA) had approved the use of ultrasound with microbubbles for diagnostic applications (Durot et al. 2018). While some of these proposed innovations are undergoing clinical trials, some are clinically being used either as ultrasound contrast agents or for ultrasound-triggered drug release.

One such emerging frontier is the usage of microbubbles, in conjunction with ultrasound strategies. Commercially available microbubbles range from 1-8 μm in size and consist of a gaseous core surrounded by a phospholipid shell (Walker et al. 2020). Microbubbles thus are an interesting area for researchers and show promising applications in the field of molecular imaging, diagnostic and theranostics (Yeh and Kang 2012).

Ultrasound nanosensors offer several advantages including, higher sensitivity and selectivity with small sample size, low response time, portability and cost-effectiveness, which are promising to clinicians (Salvati et al. 2015). Nevertheless, reproducibility, complexity in production process, poor performance with biological fluids, biocompatibility issues, safety concerns and restriction with whole body imaging (Sivasubramanian et al. 2014) are some of the limitations that need to be positively dealt to expedite the development of clinically relevant devices. While several nanosensors have been developed for optical, photoacoustic and magnetic resonance imaging (MRI) modalities (Rong et al. 2019), the development of ultrasound nanosensors was hindered due to technological challenges, some of which have been highlighted above.

Ultrasound nanosensors shape the base for crucial research and technical advances in a number of fields, including medicine and physiology (Agrawal 2015). Figure 1 offers an overview of various biosensing components, and the process of detection beginning with the application of ultrasound waves and amounting in the generation of an output.

Nanoscale sensing, intelligent drug delivery, body area networks and other industrial and environmental control technologies are some of the most relevant applications, which have been touched upon in further sections (Khan et al. 2020). For medical and physiological applications, such technologies and tools may be built to communicate with cells and tissues at a molecular or sub-cellular stage; allowing a degree of interaction between technology and biological structures which may not have been previously achieved (Kosareva et al. 2020).

Owing to their unique size-dependent physicochemical properties, nanometre scale materials have recently become attractive biosensing candidates as they offer unique insights in real-time changes of core physiological parameters, in combination with more traditional sensing techniques (Guo et al. 2023). Nanosensors have been harnessed for (a) drug delivery to challenging areas (b) detection of cellular biomarkers playing important roles in pathogenesis, and (c) measurement of moieties at nano-scale concentrations. Recently, a wide variety of applications of nanosensors have been documented across the pharmaceutical, medical and industrial sectors (Vogel 2019). In the sections that follow, an overview of material considerations, potentials for combination with nanocarriers,

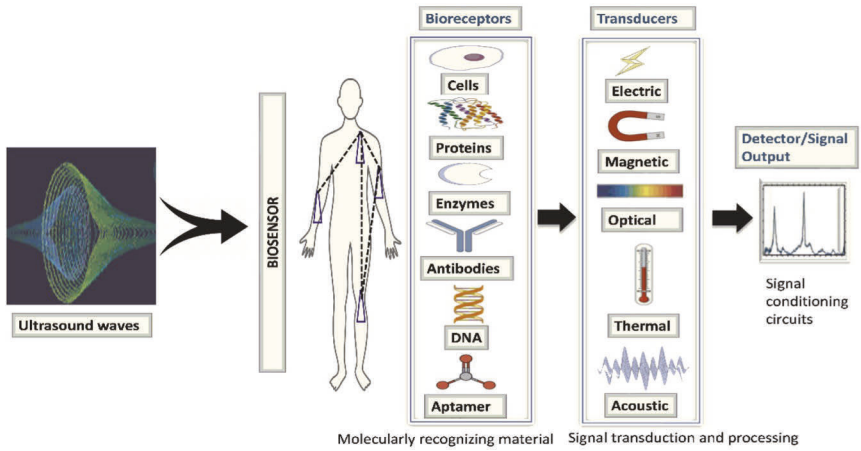

Fig. 1. Schematic representation of Biosensor components. ⏎

key factors influencing performance and clinical translation have been touched upon. This has been done in an attempt to provide readers with a well-rounded perspective of the ever-evolving domain of ultrasound nanosensors.

Types of Materials Used for Fabrication of Ultrasound Sensors

Ultrasonic sensors are typically constructed using piezoelectric elements, comprising a transmitter (responsible for sound wave transmission) and receiver (reflected back from an object or person) (Chu and Cetin 2022). Traditionally, materials such as quartz, barium titanate and lithium sulphate were used, however, they are no longer employed for their acoustic benefits (Noce 1990). Newer piezoelectric materials, such as lead zirconate titanate, lead metaniobate (Kergosien et al. 2023) and co-polymers such as polyvinylidene fluoride (PVDF) are now increasingly utilized (Westphal et al. 2023). They offer advantages such as higher acoustic impedance, in comparison with metallic or ceramic solids. Additionally, there has been an emergence of composite materials, offering a high coupling coefficient. Their properties may be understood to lie somewhere between ceramics and polymers, with their structure comprising of parallelly arranged ceramic rods, embedded in a resin matrix (State et al. 2010). With respect to the construction, piezoelectric crystals, offering a host of unique electromechanical properties, are connected to the front end of the transducer. On the application of an electric current, they begin to vibrate, thereby generating ultrasonic waves, brought about by an energy conversion (Bachu et al. 2021).

Ultrasound Sensing in Combination with Other Carriers

Ultrasound-guided sensing is an evolving theranostic technique, which helps to monitor drug carriers, trigger drug release and enable the improvement of drug deposition with high spatial precision (Sirsi and Borden 2014). As soon as ultrasound radiation enters the body, it starts interacting with the cells and the engineered nanoparticles that are circulating in the blood stream or residing in the extracellular matrix, thereby offer potentials in drug delivery (Fang et al. 2021). One widely explored domain has been that of neoplasm management. The impact of ultrasound interactions on nanoparticles and cells facilitates drug delivery for the management of cancer and increases the efficiency of therapy synergistically. The process by which ultrasound may be used to initiate drug release from nanoparticles is termed as ultrasound-mediated drug release (Al Sawaftah and Husseini 2020). In addition to this, ultrasound drug delivery loaded with nanoparticles may be utilized to resolve several drawbacks linked with conventional cancer treatment, owing to the ability of this technique to allow site-specific drug release, reducing the dosage required and protecting healthy cells (Tharkar et al. 2019). Several nanocarriers such as micelles, liposomes, solid-lipid nanoparticles, mesoporous silica nanoparticles and perfluorocarbon containing nanoparticles were used in combination with ultrasound to enhance the efficacy of treatment (Sawaftah et al. 2021). Some of these emerging strategies have been discussed in the following sub-sections, to provide readers a bird's-eye view of the developments in the domain.

Micelles

Micelles are self-assembled colloidal structures composed of amphiphilic molecules in an aqueous solution (Xu et al. 2015). They are made from a hydrophilic outer shell which prevents engulfment by the immune system, making them useful for targeted drug delivery, mainly for cancer therapy (Hanafy et al. 2018, Tharkar et al. 2019). Micelles have gained considerable attention as an interesting drug delivery system, owing to the simplicity in fabrication and ability to load a wide variety of insoluble drugs (Yang et al. 2020). These carriers are sensitive to external stimuli such as ultrasound and provide tremendous capability for controllable mechanisms of drug delivery (Jain et al. 2018). Several studies have shown the capability of ultrasound waves to breakdown micelle-based nanocarriers, thus permitting the diffusion of drugs at the tumor site (Husseini and Pitt 2008). Ultrasound has been harnessed as a trigger for drug release, offering benefits such as improved selectivity and potential for a synergistic effect alongside conventional therapies (Mukhopadhyay et al. 2021). While a majority of applications revolve around cancer

management, other avenues where such systems have been explored include tissue engineering, transport of agents across the blood-brain barrier (BBB) for the management of neurological disorders (Chandan et al. 2020) as well as gene delivery (Movassaghian et al. 2015).

Liposomes

Liposomes are mainly used as carriers for *in-vivo* drug delivery because of their in-built biocompatibility properties and versatile features (Abu Lila and Ishida 2017). These drug carriers typically have a diameter of about 100-200 nm and are composed of an aqueous core surrounded with a self-assembled bilayer lipid membrane (Zhigaltsev and Cullis 2023). Various studies have reported that the application of ultrasound can induce the release of drugs from liposomes, even though the key mechanism of drug release remains largely unknown (Schroeder et al. 2009, Sirsi and Borden 2014). Many pathways are likely to be involved and the prevailing mechanism of drug release relies on specific ultrasound parameters and chemical composition of the liposomes. Cavitation, thermal effects and acoustic streaming are the potential mechanisms for drug release from liposomes using ultrasound (Wang et al. 2015). In terms of recent applications, liposome-based delivery platforms have been observed to greatly improve the precision offered by ultrasound-led diagnostic and therapeutic technologies. Some noteworthy advancements include the combined benefits of liposomal and ultrasound delivery in the management of thrombolysis and controlled medication release, paving the way for the future of nanomedicine (Zhang and Fowlkes 2022). Another application of ultrasound-triggered release in conjunction with liposomes is the domain of local anaesthesia delivery (Cullion et al. 2018). Browning and colleagues proposed the formulation of iproplatin (prodrug)-loaded liposomes, which were further conjugated with microbubbles, for improved drug concentration in comparison with passive loading techniques (Browning et al. 2021).

Solid Lipid Nanoparticles (SLNs)

SLNs comprise a drug-loaded core surrounded by a solid lipid shell. SLNs have been drawing attention in drug delivery research, because they offer combined benefits of both polymeric nanoparticles and lipid structured nanoparticles, such as liposomes (Paliwal et al. 2020). SLNs have several advantages over other nanocarriers, which include high drug loading capacity, greater stability, low toxicity and suitability for brain targeting, as they cross the BBB effectively (Sadegh Malvajerd et al. 2019). Timbie and co-workers proposed that ultrasound was able to improve the efficacy of drug-loaded nanoparticles designed for penetrating the BBB, and this

may be helpful in the treatment of glioblastoma (Timbie et al. 2017). SLNs in combination with ultrasound can serve as an attractive alternative for the delivery of a drug to the brain (Sirsi and Borden 2014). However, work remains to be done in the field, as there have been a small number of studies in recent times to support the conjunction of these systems.

Mesoporous Silica Nanoparticles (MSNs)

Biocompatible MSNs are inorganic nanosystems that have the potential to generate molecular imaging, drug delivery and biosensors with high accuracy (Tang et al. 2012). Wu and co-researchers successfully loaded MSNs with doxorubicin, which were successfully targeted into the brain at the tumour site. They were then simultaneously activated by focused ultrasound exposure, which displayed substantial inhibition of the progression of brain tumour (Wu et al. 2018). Another study shed light on the ultrasound-mediated uptake of MSNs, as a smart delivery system. This proposition was centered around the difference in surface characteristics across different stages of the journey to tumour cells, ultimately resulting in the exposure of the positively charged surface on detachment of the outer polymeric shell. This step, in turn, positively influences the internalisation of the therapeutic agent by tumour cells (Paris et al. 2018). Over time, dual-responsive systems have also been designed, functioning on a combination of pH and ultrasound triggers. These systems have been pitched as the future of cancer management, offering potentials for combining conventional chemotherapeutic approaches with photothermal therapy (Li et al. 2018).

Perfluorocarbon (PFCs) Containing Nanoparticles

PFCs are inert and heavily fluorinated organic materials that are capable of dissolving huge amounts of gases including oxygen (Li et al. 2018). PFCs are marked by unique characteristics, which include chemical and biological inertness. In a study, it was stated that micrometre-sized PFC droplets could be vaporized into gas bubbles by applying ultrasound (1.5–8 MHz). This process is known as acoustic droplet vaporization (ADV). This led to the formation of microbubbles, which may act as contrast agents in ultrasound diagnostics (Matsunaga et al. 2012). Biomedical applications of PFC encompass usage as a substitute for lung surfactants and applications in several ophthalmology-related conditions. Numerous colloidal PFC formulations are being evaluated for molecular imaging and targeted drug delivery using ultrasound radiations and magnetic resonance, and it is anticipated that a greater number of studies, moving forward, would pave the way for clinical translation on a larger scale (Borden et al. 2020).

Parameters Influencing the Applications of Ultrasound Sensors

Certain parameters like frequency, intensity, mechanical index, pressure variation and duration of ultrasound exposure may affect the efficiency of ultrasound nanosensors and thus impact the effectiveness of ultrasound-mediated drug delivery and other therapeutic applications (Araújo Martins et al. 2021). The sub-sections that follow offer a brief insight into each of these major factors, providing an overview of various factors that must be monitored while designing and utilizing these systems.

Frequency

For various research studies, ultrasound frequency may be modulated as it is based on the cell type and the animal model chosen for experimentation. It is mainly used for its therapeutic applications rather than diagnostics (Daftardar et al. 2019). Cavitation is the process in which liquid or gas cavities are formed and undergo growth (chiefly in the form of microbubbles) when exposed to acoustic radiation, which leads to tissue damage. Cavitation effect arises due to increased levels of frequency. Hence early detection of impact of cavitation is an important factor to avoid unintended side-effects, and for the adjustment of ultrasound frequency and intensity (Izadifar et al. 2019). Lower levels of ultrasound frequencies have a lower attenuation effect that allows it to easily penetrate into deeper tissues for required therapeutic effect. Lower ultrasound frequency (i.e., frequency lesser than 1 MHz) is generally used for therapeutic purposes. Higher frequency results in lower penetration due to its high resolution. Microbubble cavitation is intensified when ultrasound frequency is near or equal to resonance frequency of the microbubbles (Vignon et al. 2013). Thus, studies have elucidated that the frequency applied is a crucial factor in governing specific applications of such devices.

Intensity

Ultrasound energies that are generally more than the threshold of cavitation can thermally and sonochemically induce permanent damage to lipid membranes and result in protein/DNA denaturation. Thus, high intensity ultrasound can initiate heating effects that may modulate tissue function (Peek and Wu 2018). As per the guidelines issued by the FDA, the heating of tissues exposed to ultrasound should not result in a rise in temperature over 1°C. Nonetheless, higher intensity ultrasound can be utilized when pulse length and pulse repetition frequency values are reduced (Tharkar et al. 2019). Additionally, higher energy ultrasound can enable tissue hyperthermia and thermal ablation which can be

beneficial in eradicating damaged tissues (Kim et al. 2020). While a majority of applications on this front remain limited to tissue healing and regeneration, more focused research could potentially expand the current scope of therapeutic applications.

Mechanical Index (MI)

MI of ultrasound is directly proportional to acoustic pressure; hence MI may be employed as a substitute to ultrasound intensity. Higher cavitation is indicative of higher MI; hence cavitation produced can be easily determined by MI. For ultrasound energy, the MI limit should be in the range of 0.2 and 1.9. As per the FDA recommendation, in order to protect tissue damage, the highest range of MI should not exceed 1.9 (Cunitz et al. 2017). Some applications of MI modulation include cardiovascular applications, such as thrombolysis, improving of ischemic conditions as well as the delivery of genetic material, such as nucleic acid (Porter et al. 2021). Advances in clinical radiology also include contrast-enhanced ultrasound imaging, at a high MI value, for portal hypertension monitoring (Gao et al. 2020).

Duration of Ultrasound Exposure and Pressure

The duration of treatment in ultrasound assisted drug delivery and therapeutic ultrasound depends on the time required for the ultrasound to produce intended effects. The period of ultrasound treatment can be determined by variables like situation and type of tissues undergoing treatment (Bull et al. 2013). High pressure ultrasound waves lead to undesirable effects in the body and can cause inertial cavitation, nevertheless treatment over a longer duration may improve drug delivery. Lower pressure demands stable oscillations of microbubbles, which is desired for successful drug delivery. Precise treatment time period in research protocols is crucial for determining various applications (Joshi and Joshi 2019, Schroeder et al. 2009). Short-duration, focused ultrasound exposure has been utilized for the regulation of protein expression. Kruse and co-workers demonstrated its usage in regulating the expression of heat-shock proteins, chiefly Hsp70, to map thermal damage. The key take-away from the study was the potential for utilizing focused ultrasound energy in the maintenance of cellular integrity, in response to stresses (Kruse et al. 2008). On the other hand, longer exposure has been assessed for its benefits in reperfusion therapy. The key advantages in sonoreperfusion therapy stem from a longer circulation time, owing to microbubble-mediated delivery (Chen et al. 2023).

Nanotechnology Based Modification of Ultrasound Nanosensors

Nanotechnology plays a vital role in designing biosensors for revolutionizing the healthcare industry. Biosensors have benefited significantly from advancements in nanotechnology. Tremendous progression in this field is due to the demand for rapid, sensitive and cost-effective biosensors (Dewan et al. 2016). Nanosensors, nanoprobes and nanosystems, owing to their ability to analyze multiple substances rapidly, have revolutionized the field of chemical and biological analysis (Huber et al. 2015). Sensors have the ability to detect virus particles or even low concentration of substances that could have adverse effects. Nanosensor is employed for measuring atomic scale data and can transfer it to obtain data that can be quickly analyzed (Zeid et al. 2023).

Nanobiosensors are made up of nanomaterials, which can identify the nanoscale events and improve sensitivity and performance. Nanomaterials are a gift to nanotechnology, which have dimensions between 1–100 nm (Haddad et al. 2018). Widely used nanomaterials include nanotubes, nanowires, and thin films made up of crystalline matter. Nanomaterials are incorporated into transducers or receptors to enhance detection capability and sensitivity. Advances in nanotechnology used in ultrasensitive devices is a promising way to solve problems related to medical diagnosis (Sharifi et al. 2019).

Advantages of Nanotechnology-Based Biosensors

- Detection of target molecules, a key factor in early detection of diseases such as breast cancer (Sharifianjazi et al. 2022).
- Positive impact on ultrasensitive devices for the possible analysis of mycotoxins.
- Detection of pathogens from the environment.
- Toxicity analysis (Castillo-Henríquez et al. 2020).

Biosensors chiefly comprise two components, a bioreceptor and a transducer element to convert physiological information into measurable effect. Due to the high specificity of bioreceptors, biosensors are more selective than chemical sensors. Biosensors have been explored in the early detection of cancer as well as various other diseases. They may also be used to detect specific types of DNA. The small size of such sensors makes administration via the transdermal route possible (Agrawa 2015).

Nanosensors consist of bio-sensitive layers containing biological recognition elements, which are covalently attached to the transducers.

Biological sensing elements are biological molecular species such as an antibody, an enzyme, DNA or living cells which use biochemical mechanism for recognition (Vo-Dinh 2008, Karunakaran et al. 2015). Two broad types of receptors include affinity-based nanosensors and catalytic-based nanosensors. Affinity-based nanosensors are used to bind to the molecules of interest whereas, catalytic-based sensors bind to the molecule of interest by a catalyzed chemical conversion (Devrees 2007). They act by charge transfer between molecules and sensitive materials resulting into a signal (Yonzon et al. 2005). The aim of developing a recognition method is to have a sensor with high degree of selectivity for the analyte.

Applications of Ultrasound Nanosensors in Diagnosis and Drug Delivery

Ultrasound nanosensors have been utilized in CNS imaging, more specifically with respect to the monitoring of neurotransmitter activity. When positioned at release sites, they have been harnessed for the purpose of providing an insight into the diffusion profiles of these agents (Del Bonis-O'Donnell et al. 2021). Advancements in nanosensor technology have paved the way for new avenues in the domain of regenerative medicine. In addition to other types of nanosensor such as magnetic and fluorescence nanosensors, ultrasound nanosensors offer a cost-effective alternative to facilitate imaging. Some potential areas of application include loading of nanoparticles onto these sensors to locate cells as well as elucidate their function, through the emission of signals.

In a study undertaken by Walker and colleagues, a solid-state ultrasound contrast agent was utilized, for *in vivo* modulations in pH. The development of such contrast agents, which permit the detection of a variety of biomarkers, is a challenge. Using gas-filled microbubbles with a silica core and a coating of a pH-responsive polymer, an ultrasound nanosensor was developed. Its activity was further monitored in a mouse model, yielding a positive outcome and supporting its usage in the enhancement of the functioning of contrast media (Walker et al. 2020).

Zhang and colleagues assessed the functionality of a nanomotor device combining optical and ultrasound principles. A major challenge is the extent to which these systems may be capable of mimicking biological systems. The aggregation of these devices in the acoustic field and subsequent separation on application of irradiation was studied, providing insights on how the modulation of physical conditions may be used to govern the distribution and transport of nanosystems within biological systems (Zhou et al. 2018). The data gleaned from this study may find applications in various domains, such as imaging and controlled drug delivery.

Matrix metalloproteinases, chiefly matrix metalloproteinase-9 (MMP-9) play a significant role in determining the extent of cellular infiltration and tumor proliferation. DNA aptamers have been used for highly selective targeting of cancer cells. Kim and colleagues utilized an ultrasound-led, gold nanosphere system bound for the tumor microenvironment in a breast cancer model (Kim et al. 2022). The results obtained warrant further research to establish safety and efficacy, and subsequent translation to clinical settings. Table 1 showcases encapsulation of some recent applications of ultrasound technologies, in drug delivery and diagnostics.

Bench to Bed-Side Translation

Ultrasonic nanosensors are gaining attention and acceptance in the detection and management of a variety of disease conditions, chiefly those with complex etiologies. One such example is their usage in the detection of inflammatory markers such as interleukins, which may reveal the extent of damage caused in conditions such as rheumatoid arthritis and cardiovascular complications (Hosseinikhah et al. 2021). In addition to diagnosis, their role has also been elucidated in enhancing drug delivery.

A noteworthy advancement has been the application of ultrasound-based nanosensors in the detection of metastases. Luke and coworkers developed a sensitive method for the detection of lymph node tumors, using nanosensors functioning on the photoacoustic principle. The nanosensor was targeted to the epidermal growth factor receptor, enabling the non-invasive, highly specific detection of tumor proliferation (Luke et al. 2014). Continuing the discussion with respect to cancer, photoacoustic imaging has also been utilized in detecting pancreatic cancer. Nanosensors loaded with dyes such as pentamethine cyanine have been utilized, and the hybrid usage of photo and acoustic signaling has been observed to significantly improve the sensitivity and stability of such contrast media (Laramie et al. 2021).

Chronic drug therapyhfaces several challenges, prompting researchers to explore strategies such as personalized medicine. Nanosensors utilizing acoustic principles have been utilized to detect and monitor concentrations of drugs such as lithium in the bloodstream, overcoming drawbacks of less sensitive systems such as fluorescence microscopy. Minor changes in analyte concentrations may be detected in deep tissues, and these systems are being constantly worked upon, in order to permit the detection of a wider range of analytes (Cash et al. 2015a). Nanosensors responsive to nitric oxide have also been developed combining shortwave infrared dyes and acoustic principles, enabling visualization of drug-induced hepatic injury (Rathnamalala et al. 2023). At a cellular level, the detection of various elemental moieties is crucial, as a disruption in their levels may

Table 1. Recent update on the application of ultrasonic nanosystems in therapy and diagnostics. ⏎

Agent and mode of delivery	Model used	Observations and conclusion	References
Protein delivery, through perfluorocarbon nano-droplets	*In-vitro* mammalian cell model	Using ultrasound mediated vaporization, proteins were delivered to cells through endocytosis. On combination with ultrasound, an enhanced delivery of the cytotoxic agent was achieved. This may indicate potentials for applications in apoptosis and cancer management.	(Yamaguchi et al. 2023)
Nano-lipid contrast agent, guided by ultrasound	Human breast cancer cell line T47D	Combination with ultrasound improved the viability of self-healing cells, showcasing synergistic benefits. Safe and effective methods for apoptosis induction in cancer cells.	(Yuanyuan Zhang et al. 2022)
Paclitaxel loaded onto PLGA nanobubbles, in combination with ultrasound	SKOV-3 and HEK293T cell lines	Improvement in biocompatibility, enhanced imaging by ultrasound application, integration of therapeutic and diagnostic benefits.	(Li et al. 2017)
Doxorubicin in combination with nanodroplets and focused ultrasound	Breast cancer cell line MDA-MB-231	Enhancement of drug distribution within the tumor, inhibition of cellular proliferation, potential for improved efficiency in cancer management through combination with ultrasound.	(Cao et al. 2018)
Nitric oxide loaded onto silica nanoparticles, in combination with focused ultrasound	Pancreatic cancer cell line PANC-1	Greater retention of nitric oxide, exertion of a more potent inhibitory effect on tumor growth, thereby improving overall survival.	(Zhang et al. 2016)
Gemcitabine and miR-21 inhibitor loaded onto gold nanoparticles, in combination with low-frequency ultrasound	Pancreatic cancer cell line SW1990	Improvement in cellular permeability, reduction in tumor volume, improved perfusion. Using co-delivery, a significant enhancement in therapeutic outcomes may be achieved.	(Lin et al. 2018)
Alginate-stabilized doxorubicin-loaded, multifunctional stimuli-responsive perflourohexane nanodroplets	Breast cancer mice model	Controlled, triggered drug release and ADV-mediated destruction of tumor cells, characterized by tumor regression. Served as contrast-enhanced ultrasound imaging agent.	(Baghbani et al. 2016)

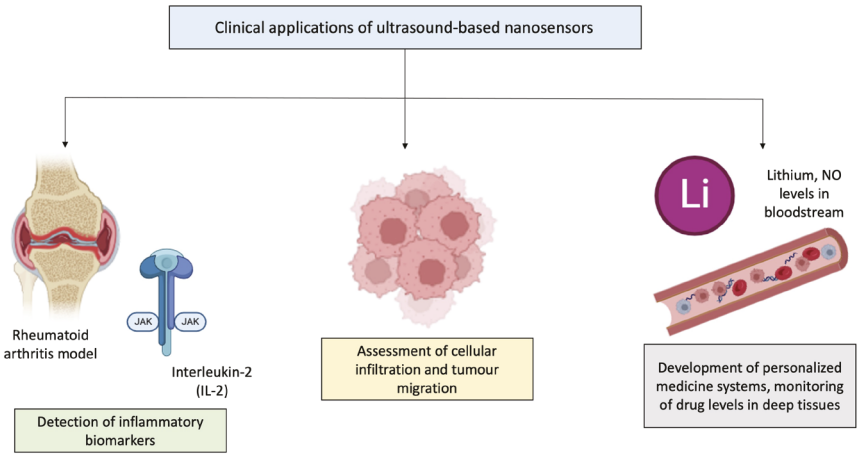
Clinical applications of ultrasound-based nanosensors
Rheumatoid arthritis model
JAK
JAK
Interleukin-2 (IL-2)
Detection of inflammatory biomarkers
Assessment of cellular infiltration and tumour migration
Li
Lithium, NO levels in bloodstream
Development of personalized medicine systems, monitoring of drug levels in deep tissues

Fig. 2. Clinical applications of ultrasound-based nanosensors (created using Biorender).

trigger several pathogenic mechanisms. Huang and colleagues explored the usage of targeted carbon dots in the monitoring of copper levels in the endoplasmic reticulum (ER), a critical determinant of ER stress (Huang et al. 2022). The results obtained were promising, offering an ease in detection over conventional systems. Figure 2 offers an overview of the clinical applications of ultrasonic nanosensors.

Conclusion

As discussed at length over the course of the chapter, recent research advancements largely focus on the design and synthesis of multi-functional nanocarriers for drug delivery and imaging. Ultrasound has been pitched as an attractive trigger for remote, non-invasive drug release from nanocarriers, in response to a stimulus. By undertaking a combination of ultrasound and nano-scale carriers, a new therapeutic modality of ultrasound-mediated drug release has gained attention steadily (Moradi Kashkooli et al. 2023). However, a major challenge that must be addressed in the development of such systems is the need for constant improvement. This is primarily done in order to bring about an improvement in sensitivity and responsiveness (Xia et al. 2016). In order to ensure this, there is a need to further our understanding of interaction mechanisms between the source of the ultrasound signal and nanocarriers, such as the thermal effect, cavitation, and target-site degradation, some of which have been briefly touched upon. Another challenge associated with ultrasound theranostics is a potential roadblock with respect to the differentiation of tumours, which may complicate the imaging of soft tissues (Wagner et al. 2019). Additionally, with respect to ultrasound

imaging, there is a challenge in terms of creation of reference maps, as a standard that test results must be compared with, to ensure precision of assessment (Wilhjelm et al. 2006). Before furthering efforts in the domain of nanotechnology, it is essential to address these pitfalls with respect to the primary source of energy, i.e., ultrasound.

Moving forward, certain challenges with respect to nanocarriers warrant attention as well. While they offer a number of advantages such as improved drug solubility, lowered side-effects and improved targeting (Mittal et al. 2021) as previously discussed, some limitations exist. A primary challenge with respect to nanocarriers is the lack of standardization and a well-defined regulatory framework, which becomes complicated in the case of specialized systems such as exosomes. In addition to this, there is a massive focus on oncology as a discipline, however, there it is prudent to explore other disease conditions that may benefit from nanomedicine as well (George et al. 2022). While results from preclinical studies have been promising, there is a need to undertake clinical testing in diverse populations, to obtain a bigger picture (Tyag and Sants 2018). Owing to high production and translational costs of some of these nanosystems, they are often high priced, limiting access to patients. This becomes especially complicated in instances of adjuvant therapies, wherein such therapies are combined with approaches such as chemotherapy and immunotherapy, for cancer management (Huan and Zho 2020). The authors have attempted to offer a perspective on the challenges posed in the implementation of ultrasound technologies and nanosystems, both, independently and when used together. Given the growing focus on healthcare equity and improved market access across the globe, there is a pressing need for research initiatives to focus on these fronts, for a healthier tomorrow.

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6

Advances in Hybrid Biosensor and Application in Drug Delivery System

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Introduction

Biosensors, which use biological components to detect and monitor an environment, have various benefits. Biosensor development can take advantage of the highly sensitive nature of biological materials to directly detect the presence or absence of analytes based on their effects on cellular metabolism (Shanbhag et al. 2023). Using Biosensors it is possible to screen wide range of toxins with quick response and great sensitivity. Furthermore, cell type selection can provide some degree of selectivity (Ahmed et al. 2014).

Cellular metabolism is the orchestration of the chemical and enzymatic events that make up a cell's life cycle. These reactions comprise a wide range of chemical and enzymatic reactions associated with cell growth and maintenance (Ding et al. 2020, Liu et al. 2015). We need to consider the wide range of functions that a cell performs, including DNA replication, DNA transcription, RNA translation, macromolecule digestion, macromolecule

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construction, and monitoring of the extracellular and intracellular milieus, to gain a thorough understanding of the complexities of cellular metabolism (Seok et al. 2021, Liu et al. 2017).

Within a functioning cell, chemical and enzymatic events take place concurrently. Furthermore, none of these reactions happen in a vacuum; rather, the outcome of one or more reactions controls the rate at which each reaction proceeds (Mukhopadhyay et al. 2024, Šponer et al. 2018). All things considered; a huge network of interconnected cellular processes underpins the organization of cellular metabolism. Because of this interdependency, it is clear that analytes that influence one or more facets of cellular metabolism are likely to affect the characteristics of the cell, such as membrane conductance and capacitance, impedance, as well as action potential parameters, such as action potential rate, amplitude, and shape (Ray et al. 2016, Niebur 2008).

The aforementioned benefits make biosensors that contain live, complete cells also known as hybrid biosensors, commercially significant in several applications. These biosensors, for instance, are especially helpful in the detection of chemical and biological warfare (CBW) weapons. Additionally, biosensors could enhance current pharmaceutical screening techniques. It's feasible that animal testing used in pharmaceutical screening will be eliminated, or at least drastically reduced, thanks to this kind of biosensor technology (Mehrotra 2016, Pohanka 2023, Lim et al. 2005).

A few advancements in the field of hybrid biosensor technology have been documented in scholarly works. Giaever and Keese, for instance, have provided methods (in collaboration with others) for tracking the impedance properties at cell/electrode interfaces (Hucklesby et al. 2021). However, a single cell cannot cover the entire area of the wide area (e.g., 250 μm diameter) electrodes used in the systems described by Giaever and Keese. Consequently, the parallel impedance of the exposed electrode area and the impedance of cell-cell contact areas (caused by the space between neighboring cells) obstruct the precise determination of the impedance characteristics of a single cell (Asphahani et al. 2011, Alexander et al. 2013). Furthermore, Giaever and Keese's work only reveals alterations in cell motility. Furthermore, the capacitance and conductance of cellular membranes are described as being constant, and any variations in these parameters are explained in terms of changing the area of the cellular membrane (Hucklesby et al. 2021).

A system resembling the one described above was employed, coupled with a different method that utilized electrodes smaller than the cell to be watched. 'Single Cell Mobility and Adhesion Monitoring Using Extracellular Electrodes' Biosensors and Bioelectronics, 6, 359-67 (1991). Generally large-area electrodes were employed in both systems (Lind et al. 1991). This method was limited to monitoring cell motility by means

of impedance variations; nonetheless, it made it possible to examine single-cell effects devoid of the previously noted shunting effects. Additionally, it was believed that the membrane conductance and capacitance in these systems would always remain constant (Ghenim et al. 2010).

Therefore, a method that makes use of electrodes that are smaller than the diameter of a cell while still allowing for the monitoring of variations in the capacitance and conductance of the cellular membrane is still required. This method would also allow voltage-gated ionic channel conductance to be monitored. Furthermore, substances that alter a cell's impedance, action potential parameters, membrane conductance, membrane capacitance, and cell/substrate seal resistance could be found and tracked using such a technique (Römer and Steinem 2004).

Among other ion channels, voltage-gated Na+ channels contribute to the electrical excitability of nerve cells and their ability to conduct action potentials. A brief stimulus can partially depolarize the membrane of a cell containing multiple Na+ channels, which causes some of the channels to open quickly and let Na+ ions into the cell. Additional channels open as a result of the positive charge inflow, further depolarizing the membrane and allowing additional Na+ to enter (Devor 2006, Mathie 1997), until the membrane potential has changed from its resting value of roughly –70 mV to the Na+ equilibrium potential of roughly +50 mV, this process keeps on repeating itself in a self-amplifying manner (Jacob and Civan 1996).

If the open channel conformation were stable, the cell would enter a new resting state with all of its Na+ channels permanently open at that time, where the net electrochemical driving force for the flow of Na+ is zero. The Na+ channels are automatically inhibited to stop the cell from entering such a prolonged electrical spasm. Now that the membrane potential has returned to its initial negative resting value, the Na+ channels gradually shut and stay closed. The whole cycle, from the first stimulus to the return to the initial resting state, takes a few milliseconds or less (Dudel 1978).

Voltage-gated K+ channels in the plasma membrane speed up the healing process in many, but not all, types of neurons. These channels respond to membrane depolarization by opening similarly to the Na+ channels, however they do so more slowly. The K+ channels assist in quickly bringing the membrane back near the K+ equilibrium potential and restoring it to its resting state by boosting the membrane's permeability to K+ at the exact moment that the Na+ channels are closing due to inactivation. The K+ channels close once more as a result of the membrane repolarizing, which also permits the Na+ channels to reactivate after being inactivated. This allows the cell membrane to be prepared for a second depolarizing stimulation in less than a millisecond (Kim and Nimigean 2016).

When one looks at the membrane potential in relation to time, one may observe that an action potential has different properties, such as shape, amplitude, and rate of depolarization (if cells spontaneously depolarize). The frequency at which a cell generates an action potential (rapid depolarization) is referred to as its action potential rate. The height of the peak depolarization that happens during an action potential is referred to as its amplitude. The depolarization and repolarization time courses are referred to as the action potential shape (Huxley and Stämpfli 1951).

Additionally, an apparatus for cell monitoring that uses an electrode array with a reduced electrode diameter and low electrode impedance is needed in the state of the art, in order to detect and track changes in each individual cell's cellular membrane (Dong et al. 2021).

Principle of Hybrid Biosensor

Any device that receives a signal or stimulus and produces an electrical signal in response is referred to as a sensor. The signals that are emitted are indicative of electrical signals that are easily measurable, like voltage or current. The analyte and biological material interact to create a bound analyte, which produces an electrical response that can be measured. On rare times, the analyte may change into a product that releases heat, hydrogen ions, gas (oxygen), or electrons. The standard components of a biosensor are an electrical system with a signal amplifier, processor, and display; a transducer component made of semi-conducting material or nanomaterial; and a bio-receptor (such as an enzyme, antibody, cell, nucleic acid, or aptamer). Transducers and electronics may be integrated, as demonstrated by CMOS-based microsensor devices (Perumal and Hashim 2014, Zhang et al. 2017, Polatoğlu et al. 2020, Han et al. 2007). Figure 1 is the schematic diagram of the principle of a hybrid biosensor.

Methods to Develop a Biosensor

Method 1

One stage in the process of developing a biosensor involves building a monolithic device that consists of a range of planar microelectrodes organized on a substrate and linked to a conductive pattern with contact points attached to it within a cell culture chamber. The other method involves growing cells in a medium that is supplied inside the cell culture chamber, where the diameter of the cells is larger than the diameter of a microelectrode; growing the cells; applying a signal to each microelectrode separately in relation to a reference electrode submerged in the medium;

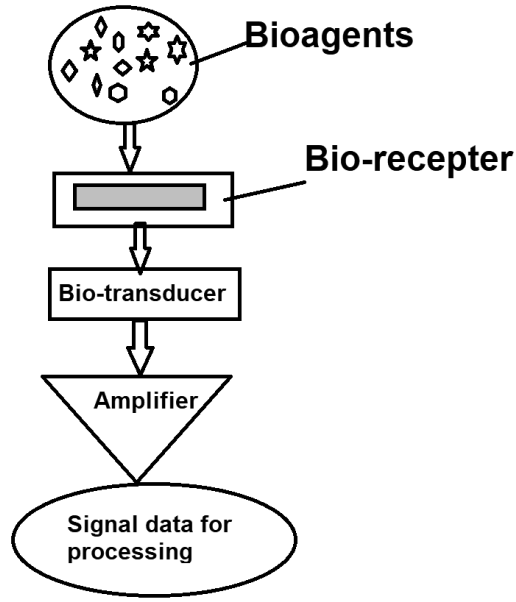

Fig. 1. Schematic representation related to the principle of hybrid biosensor.

observing the signals generated by applying an electrical signal between the reference electrode and the microelectrodes; and keeping an eye on the characteristics of the cells adhering to the individual microelectrode surfaces, including impedance, action potential parameters, cell membrane capacitance, cell membrane conductance, and cell/substrate seal resistance. After that, these characteristics are ascertained by measuring the impedance values that are derived from the generated signals (Vigneshvar et al. 2016, Zhang et al. 2017, Lee et al. 2018).

Method 2

To monitor the effects of an analyte in vitro, one can follow these steps: placing a monolithic device with a substrate-arranged array of planar microelectrodes in a cell culture chamber; attaching the microelectrode array to a conductive pattern via contact points attached to it; growing cells in a medium that is provided in the cell culture chamber, where the diameter of a cell is larger than that of a microelectrode. To monitor the effects of an analyte in vitro, one can follow these steps: installing a monolithic apparatus with a substrate-arranged array of planar microelectrodes in a cell culture chamber; attaching a conductive pattern with contact points attached to the array of microelectrodes; growing

cells in the media that is provided in the cell culture chamber when the diameter of a cell is larger than the diameter of a microelectrode (Hosu et al. 2019, Mun et al. 2015, Kim et al. 2016).

Application of Biosensors in Drug Delivery

Applications in Diabetes

Diabetes is one of the most well-known diseases in the world. This condition presently affects approximately 500 million people worldwide, and by the end of the decade, that number is predicted to rise to 75%. Diabetes is often classified into three types: Type 1 (formerly known as juvenile diabetes); Type 2 (sometimes characterized as adult-onset diabetes); and gestational diabetes. About 2–10% of pregnant women get gestational diabetes, and in about 50% of these cases, the mother gets type 2 diabetes after giving birth. Typically, 5–10% of diabetes cases are T1D instances, with the remaining 90–95% being T2D cases. For the benefit of persons suffering from T1D or T2D, blood glucose monitoring is essential to their overall health and well-being. As crucial, if not more so, is the requirement to give the required medication as soon as one's blood glucose is established. This crucial second component has been the driving force behind major efforts and eventual commercial successes in the development of closed-loop diabetes management systems (Jarczewska and Malinowska 2020, Shetti et al. 2019).

Applications in Cancer Treatment

Tumor physiology differs greatly from normal tissue physiology. The features of the tumor tissue microenvironment include hyaluronidase increase, moderate acidity, high GSH concentration, and O_2 depletion, all of which can function as endogenous triggers. There is great promise for treating cancer with several bioresponsive drug delivery techniques that consider the expression of tumor-associated markers (such nucleolin and miRNA) as well as pH, redox, and enzyme reaction. For instance, compared to normal cells, tumor cells have an increased need for glucose to satisfy their energy needs for growth. Therefore, glucose oxidase (GOx) has been carefully investigated for noninvasive cancer diagnosis and therapeutics by measuring the oxygen consumption, pH changes, or production of H2O2 associated with drug release. Moreover, GOx has been used with photosensitizers, hypoxia-activated prodrugs, Fenton's reagents, and other enzymes to create multimodal synergistic cancer treatments (Ashfaq et al. 2022, Agrahari et al. 2022, Murugesan and Raman 2022, Iqbal et al. 2022).

Applications in Cardiovascular Diseases

Heart disease (CVD) continues to be the leading cause of mortality globally, despite continuous advancements in invasive cardiovascular treatments and pharmaceutical therapy. Many circulatory system problems, such as atherosclerosis and thrombosis, as well as associated clinical presentations, such as acute coronary syndrome, stroke, peripheral arterial disease, and venous thrombosis, are included under the umbrella term cardiovascular disease (CVD). A significant step toward the creation of individualized treatments that are aimed at specific diseases is the delivery of drugs on demand. The benefits of disease site-specific therapy localization and controlled medication release in the afflicted area, which minimizes off-target effects, are provided by stimuli-responsive drug delivery systems. Even though stimuli are typically categorized into three groups: physical, chemical, and biological, it is important to differentiate between intrinsic stimuli—which are typically chemical and biological and have to do with ionic strength, pH, enzymatic reactions, as well as biomechanical forces—and external stimuli, which include light, ultrasound, magnetic fields, and electrical fields. This latter class of stimuli is particularly interesting in the biomedical domain since it is not dependent on an external trigger and is more sensitive to pathogenic processes. Drug delivery strategies for CVD that are stimuli-responsive have been documented thus far, and they include hydrogels, polymers, and particles that are hydrogel-, pH-, redox-, and hypoxia-responsive (Bakirhan et al. 2018, Azzouz et al. 2021, Gupta et al. 2020, Lu et al. 2017).

Advances in Hybrid Biosensor Technology

Nanomaterial-based Hybrid Biosensors

The development of hybrid biosensors based on nanomaterials has advanced significantly, particularly with the introduction of nanoparticles, nanotubes, and nanowires. The sensitivity and specificity of biosensors are enhanced by nanoparticles such as quantum dots (QDs), silver nanoparticles (AgNPs), and gold nanoparticles (AuNPs), which offer high surface-to-volume ratios. Their unique optical and electrical properties allow for enhanced signal transduction and detecting capabilities. AuNPs, for instance, are widely used because of their exceptional biocompatibility and ability to enhance surface plasmon resonance (SPR) signals, while QDs offer unique fluorescence properties that enable multiplexed detection and imaging applications. Because of their superior mechanical strength and electrical conductivity, single- and multiwalled carbon nanotubes (CNTs) provide high sensitivity and rapid reaction times in electrochemical biosensors by enhancing electron transfer rates.

Semiconductor nanowires—such as silicon nanowires (SiNWs)—are employed in field-effect transistor (FET) biosensors to detect biomolecules in real time and without labels due to their large surface areas and high aspect ratios (Bakirhan et al. 2018, Azzouz et al. 2021, Gupta et al. 2020, Lu et al. 2017).

Bio-functionalized Hybrid Biosensors

Bio-functionalized hybrid biosensors are enhanced in functionality and selectivity by the addition of nucleic acids, enzymes, and antibodies. The catalytic activity of enzymes like glucose oxidase and lactate dehydrogenase is used by enzyme-based biosensors, which are frequently used in glucose and lactate sensors, to produce detectable signals. In order to detect toxins, infections, and disease biomarkers, immunosensors are widely employed in diagnostics. They function by utilizing monoclonal and polyclonal antibodies, which exhibit a high degree of antigen sensitivity. Nucleic acid-based biosensors, or aptasensors, use RNA or DNA sequences called aptamers to selectively bind to target molecules. This makes it possible to identify proteins, small compounds, and genetic material with extreme specificity and affinity (Bakirhan et al. 2018, Azzouz et al. 2021, Gupta et al. 2020, Lu et al. 2017).

Smart Hybrid Biosensor

Smart hybrid biosensors combine reactive polymers and smart materials to create detection devices that are sensitive and adaptive. It is possible to make customizable sensors using smart materials for specific uses. For instance, electroactive polymers respond to electrical stimuli, and piezoelectric materials convert mechanical stress into electrical signals. Examples of responsive polymers that change chemically or physically in reaction to outside stimuli are hydrogels and conducting polymers. Because of their malleable and extensible properties, hydrogels are suitable for tissue engineering and controlled drug release systems. On the other hand, conducting polymers, such as polypyrrole and polyaniline, change their conductivity when analyte is bound, making it possible to monitor biological processes instantly (Bakirhan et al. 2018, Azzouz et al. 2021, Gupta et al. 2020, Lu et al. 2017).

Patents Related to Biosensors

A component of the invention focuses on using the biosensor apparatus to ascertain a polynucleotide analyte's nucleotide sequence. Biosensor apparatus is made up of an aperture in a solid-phase substrate and a protein nanopore fixed in a lipid layer. This provides a stable platform for

using the first and second members of one or more FRET pairs to generate optical signals as the labeled analyte translocates through the bore of the protein nanopore (US20130203050A1) (Jarczewska and Malinowska 2020).

A UDG template, an S-HAP1 hybrid chain, HAP2-AgNCs, and ExoIII enzymes make up the biosensor that scientists discovered for uracil glycosylase detection. This biosensor can be used to detect the activity of uracil glycosylase by using fluorescence detection, which has an excitation wavelength of 560 nm, an emission wavelength of 625 nm, and a detection wavelength band of 575–750 nm. The biosensor exhibits favorable characteristics such as high sensitivity, good specificity, mild reaction conditions, and high reaction speed; the method employs silver cluster fluorescence detection, which facilitates easy operation, short detection periods, and convenient carrying; the process cost is low, making it appropriate for the demand for low cost equipment in industrialization; the preparation method is straightforward, repeatable, and stable in performance, making it suitable for the detection of UDG in the field of medical treatment and health (CN108398406B) (Shetti et al. 2019).

Researchers have developed an iron oxyhydroxide–MoS_2A nanohybrid material, along with its fabrication method, and used it to construct an aptamer-based electrochemical sensor. This nanohybrid consists of hydroxyl ferric oxide (β-FeOOH) nanorods with MoS_2 nanosheets deposited on their surface. The MoS_2A nanosheets are synthesized via a solvothermal reaction involving phosphomolybdic acid hydrate and thioacetamide. During the fabrication process, the rod-shaped β-FeOOH substrate is vertically integrated with the MoS_2A nanosheets, forming a multi-component nanohybrid structure with uniformly distributed constituents. This advanced nanohybrid serves as the electrode material in the design of a miRNA-21 biosensor. The resulting aptamer sensor exhibits significantly improved performance, including high selectivity, sensitivity, stability, repeatability, and practical applicability for miRNA-21 detection (Ashfaq et al. 2022).

Techniques and materials for nano-biosensor-integrated hybrid microfluidic devices have been created. Paper/polymer hybrid microfluidic systems coupled with nano-biosensors for pathogen detection and infectious illness diagnostics are the focus of some embodiments (US10620200B2). Researchers created biohybrid materials with long-chain DNA aptamers that are produced from Sol-gel. The current application concerns a novel class of macroporous bio/inorganic hybrids that ensnare micron-sized concatemeric DNA aptamers. These hybrids were created using a high-throughput materials screening technique. These long-chain DNA aptamers are entrapped, which enables them to remain inside the silica material's macropores and interact with high molecular weight targets like proteins (US20180340222A1) (Agrahari et al. 2022).

Case Studies and Recent Developments

Particular Illustrations of Hybrid Biosensors in Drug Administration

Hybrid biosensors have showed considerable promise in their capacity to precisely monitor and manage medicine delivery systems. One well-known example is the use of glucose-sensitive insulin delivery systems. These gadgets provide an incredibly effective method of treating diabetes by monitoring blood glucose levels in real time using hybrid biosensors that combine nanoparticles and glucose oxidase. Another example is the development of pH-responsive hybrid biosensors for the treatment of cancer. These biosensors combine pH-sensitive polymers with nanomaterials to detect the acidic environment of tumor tissues, thereby minimizing systemic toxicity and improving therapeutic efficacy. This makes it possible for chemotherapy medications to be released precisely where the tumor is located (Lu et al. 2017).

Conclusions, Obstacles, and Prospects for Hybrid Biosensor Applications

In brief, this chapter highlights the extraordinary potential of hybrids originating from macrocycles and macromolecules to support critical biomolecule detection. These hybrids have successfully overcome several challenges, including redox behavior, cost-effectiveness, and synthetic complexity. They also show outstanding durability, precision, and sensitivity. However, further advancements are still needed, particularly when working with intricate biological matrices to achieve unparalleled sensitivity and exceptionally low detection limits. Reactants with flexible functional groups must be carefully chosen during macromolecule synthesis in order to provide sensor robustness in the face of interference and environmental perturbations.

In order to support the development of portable, wirelessly connected devices, significant steps must be taken to enable real-time detection of biomolecules in various medical conditions. Customized healthcare can be achieved through the novel advantages of hybrid sensor functionalization for multi-analyte detection over diagnostic tests, provided that biocompatibility and stability constraints are addressed. To address persistent problems with biocompatibility, stability, and repeatability, analyte-electrode interface and sensor variability optimization are required. Examining novel materials, coatings, and nanostructures provides practical ways to increase precision and effectiveness.

The use of hierarchical nanostructures seems to be a potential way to develop biosensor technology. These nanostructures provide

special advantages such as enhanced signal transduction and greater surface area, which can significantly improve biosensor performance. By combining hierarchical nanostructures to create hybrids based on macromolecules, researchers can investigate new avenues for obtaining enhanced noise control, incredibly low detection limits, and greater sensitivity in biosensing applications. Effective clinical collaboration also requires regulatory cooperation and standardization efforts. It is imperative to adopt a multidisciplinary strategy that integrates skills in material sciences, biotechnology, and engineering to optimize the use of biosensing platforms and enhance global health outcomes.

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7

Regulatory, Ethical and Legal Aspects in Healthcare and Pharmaceuticals Related to Biosensors

An Overview

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Introduction

In the recent decade, the biosensing industry has been aggressively investigated for novel uses and markets. Examples include medication screening, Alzheimer's disease diagnosis, genome sequencing, and blood nutrition monitoring (Kirsch et al. 2013, George Kerry et al. 2021). On the other hand, developing nations are in an orphan situation (Karim 2022). Although the needs of the latter are obviously very different from those of the former, many of these needs are still unmet, which suggests that biosensor applications may yet have untapped potential (Altenstetter 2017).

Two critical issues that can be addressed by technologies facilitating point-of-care testing are the inadequacy of well-equipped medical infrastructures and the recurrent necessity for decentralised testing in

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remote areas to expedite results (e.g., diagnosing infections in isolated villages or detecting pathogens in water sources).

However, in addition to technical considerations, one must also consider the lack of infrastructure and trained personnel in low-resource settings, as well as financial, regulatory, and cost considerations, in order to determine the appropriate use of biosensing devices in the healthcare sector in developing nations. In the ensuing chapters, we will outline the theoretical framework of a biosensor and evaluate the primary technological, governmental, and financial aspects that impact its possible application in addressing hygienic demands in developing nations (Altenstetter 2017).

A Biosensor 'Shell-by-Shell'

A biosensor is a device that uses one or more biologically or biomimicically derived components to identify and frequently measure a variety of targets (e.g., infections, illness indicators, physiological aspects).

There is a lot of research going on in this area in both private and academic labs, which leads to the practically daily discovery of new gadgets and uses. Following are the goals to categorize a biosensor without regard to its primary technology or intended use.

- To enable communication between the target and the device, a sensitive element is employed. To guarantee that the information is target-specific, this interaction should involve the target as little as possible in comparison to other sample parts. Given their great specificity to the most commonly requested analytes, biological molecules including DNA strands, aptamers, and antibodies are a particularly well-suited choice for this portion.
- The interface effect is transformed into a readable parameter using a transducer. These components include fluorescent molecules and functionalized surfaces, which are employed in a wide range of biosensors. Functionalized surfaces are essentially organic molecules bonded to solid materials.
- A detection system measures the signal produced by the device's interaction with the target. When the readout is optical, elements such as filters, lenses, photodiodes, and CCD cameras are often utilized; when the readout is electrical, silicon or metal components are more prevalent (Tetyana et al. 2021).
- A transporter is the entire structure that contains the other pieces. This section may also include data analysis procedures that do not require the stricto sensu biosensing stage, such as centrifugation, extraction, sorting, and other sample pre-processing steps (Bidmanova et al. 2016).

- The objective of Guiducci and colleagues proposed portable SPR sensor is to measure the amount of tobramycin, an antibiotic, filtered out of undiluted blood serum. The sensitive component is an aptamer based on the DNA. Isolated gold nano-islands, which operate as transducers when complimentary strands connect to them, are covered with several copies of this DNA strand. The detecting system can then use a photo-detector and a light source to excite and measure this change. The sample is then handled microfluidically using a glass slide as the transporter, and everything is assembled inside a plastic box.
- Sequencing lengthy DNA strands is the aim of Pacific Biosciences' PacBio RS II, which is used for gene expression measurement or mutation detection. Polymerase proteins that have been confined into nanowells make up the sensitive component. A collection of dyes used to tag individual nucleotides is known as the transducer. The transporter is a sizable structure that combines all of the hardware for analysis and opto-electronics for sensing (Chen et al. 2018, Dar et al. 2020).

Regulations and Standards: Considerations for Sensor Technologies

All sensor-based devices, especially those used in healthcare, need to be regulated in some way to guarantee the end user's safety in terms of electrical, chemical, biological, and physical aspects. The degree of risk connected with the item determines how much control is necessary. Regulations governing implantable devices like pacemakers are stricter than those governing non-invasive thermometers. It is crucial to understand the rules that apply to devices related to health, wellness, or the environment when creating or utilizing them, and to make sure they comply with those standards. In reality, it is against the law to market or sell a medical device without first ensuring that it has undergone the necessary regulatory procedures due to the possible risks associated with particular medical equipment (Haleem et al. 2021).

Standards that are domain and location-specific offer standards by which a device's quality, safety, compatibility, or interoperability can be evaluated. It is impossible to list or even define all the standards related to environmental sensors, wellness, and health in a single chapter due to their extensive nature. Any medical equipment that is intended for measurement must have sensors. Sensors can interface with gadgets like cell phones or be standalone, separate devices like home testing kits (McGrath and Scanaill 2013).

The majority of sensor-based medical gadgets work by coming into direct contact with the patient. Therefore, it is essential that the gadget does not injure the user electrically, chemically, or physically. Medically sensitive data generated by sensors needs to be communicated or stored securely. Additionally, clinical and nonclinical decisions are informed by sensor data, thus accuracy is crucial. Following rules and regulations is crucial because even the most basic sensor-based device carries a danger. Depending on whether a device is being manufactured or used for research, different regulations apply (Szabo et al. 2023).

European Market

A product with the CE mark is compliant with EU regulations and is allowed for sale inside the European Economic Area (EEA), which consists of all twenty-seven EU members, as well as, Iceland, Norway, Liechtenstein, and Turkey. The manufacturer's declaration that the product complies with the relevant EU directives is represented by the CE mark. Everything from lightbulbs to PCs to toys has this mark. The CE mark only certifies that a product satisfies all regulations to be sold in the European Economic Area, not that it is actually manufactured there. All medical equipment sold in the EU needs to have the CE mark. To achieve a CE mark, the medical device must comply with any one of the following directives (Karim 2022):

- Directive 90/385/EEC regarding active implantable medical devices
- Directive 93/42/EEC regarding medical devices
- Directive 98/79/EC regarding in vitro diagnostic medical devices

USFDA

The FDA's Center for Devices and Radiological Health (CDRH) regulates the manufacturing, repackaging, relabeling, and/or importation of medical devices sold in the United States. It also manages the control of non-medical electronic devices that generate radiation, such as color televisions and X-ray machines. The general limits set forth in the Federal Food, Drug, and Cosmetic Act apply to all medical devices (Hamrell 2006).

All medical device marketing, labelling, and post market performance monitoring are subject to these restrictions, which are outlined in Title 21 Code of Federal Regulations Part 800–1200 (21 CFR Parts 800–1200) The FDA technically 'clears' medical devices for sale as opposed to 'approving' them. The FDA's marketing clearance procedure for medical devices consists of three steps (McGrath and Scanaill 2013): (1) Verify whether the product meets the definition of a medical device under FD&C Act section 201(h). Drugs and other products that don't fit this description might be governed by separate FDA regulations in the United States. Further

regulation may be necessary for some medical equipment, such as those that produce radiation. (2) As stated in 21 CFR 860, determine the risk-based device classification: the classification will establish the degree of regulatory restrictions necessary to guarantee the device's efficacy and safety. Additionally, it will ascertain the marketing procedure (premarket notification or premarket approval [PMA]) necessary to secure U.S. FDA clearance for the product. Regardless of the risk it presents, a device is automatically labelled as a Class III (high risk) device if there isn't a substantially equivalent device. If necessary, a 'de novo' petition for reclassification from Class III to Class I or II may be filed with the US FDA. (3) Compile the information and/or data required to send in a marketing application. Premarket notification, often known as the 510(k) process, is applicable to certain Class I (low risk), Class III (high risk), and most Class II (medium risk) devices. The maker of the device must prove 'substantial equivalency' to a lawfully marketed 'predicate device' in order to prove the device's efficacy and safety. Clinical trials are rarely necessary in the 510(k) process (McGrath and Scanaill 2013).

For Class III (high risk) medical devices to be evaluated for safety and efficacy, a premarket approval (PMA) is needed. Like the new medication approval procedure, the PMA is the strictest form of device marketing application needed by the US FDA. For clearance to market, most PMA applications and some 510(k) applications need to undergo clinical trials. Compliance with the U.S. FDA's Investigational Device Exemption (IDE) regulation is mandatory for clinical studies (Hamrell 2006).

The following are the approval processes for a medical device (Fig. 1):

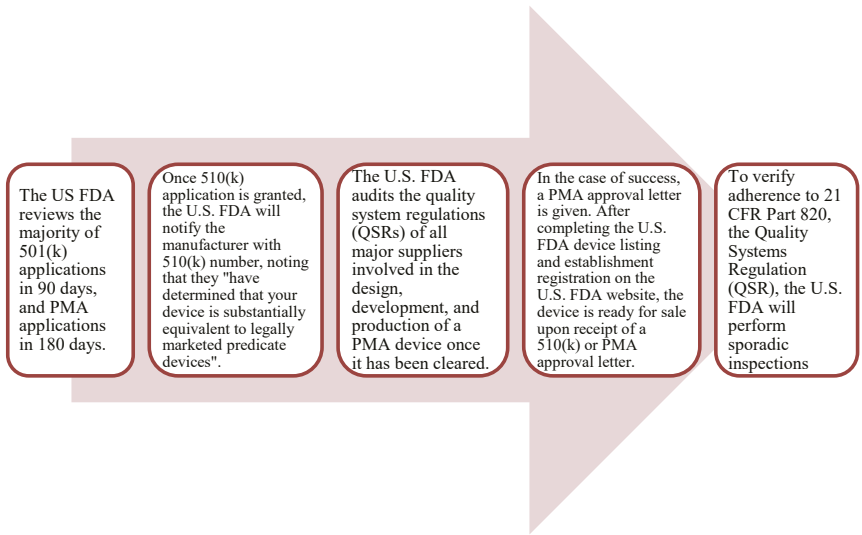
The US FDA reviews the majority of 501(k) applications in 90 days, and PMA applications in 180 days.
Once 510(k) application is granted, the U.S. FDA will notify the manufacturer with 510(k) number, noting that they "have determined that your device is substantially equivalent to legally marketed predicate devices".
The U.S. FDA audits the quality system regulations (QSRs) of all major suppliers involved in the design, development, and production of a PMA device once it has been cleared.
In the case of success, a PMA approval letter is given. After completing the U.S. FDA device listing and establishment registration on the U.S. FDA website, the device is ready for sale upon receipt of a 510(k) or PMA approval letter.
To verify adherence to 21 CFR Part 820, the Quality Systems Regulation (QSR), the U.S. FDA will perform sporadic inspections

Fig. 1. Approval process of medical device in USA ⏎

Other Medical Device Regulators

Only 65% of the 145 nations that participated in the 2010 World Health Organization Baseline Country Survey on Medical Devices have a national authority in charge of putting medical device laws into effect and upholding them. Several of the countries that have created regulations have not moved very far in putting them into practice. The World Health Organization helps nations without regulations create and put regulations into effect. The sixty-five percent of nations that have laws in place governing medical devices have different laws.

The WHO supported the Global Harmonization Task Force (GHTF), the predecessor to the International Medical Devices Regulatory Forum, and is an official observer of the latter. The EU, the FDA, Australia, and other voluntary medical device regulators have joined forces to form the IMDRF in an effort to 'fast-track the approval process of medical device internationally'. Their initial tasks include the following: (1) outlining a plan for putting into practice the uniform device identification system's internationally harmonized methodology, which was previously established by the GHTF. (2) creating a uniform set of specifications for auditing firms that conduct regulatory audits of the quality management systems of medical device manufacturers. (3) compiling a list of international standards that the members of the IMDRF Management Committee acknowledge and apply for medical device regulatory purposes (Wilson 2005).

Technological Challenges in Low-Resource Settings

Biosensors must meet a number of crucial low-resource operational requirements in order to be useful in and advantageous to developing nations. First, the suggested biosensors should require the least number of external reagents and apparatus possible due to inadequate external quality control and shaky procurement processes. Second, the outcomes must be extremely repeatable because the necessary laboratory equipment is not available to conduct control experiments. The devices should ideally function completely on their own (as a 'black-box') and robustly for a longer duration of time.

Due to the limited refrigeration and power supply capacity at distant areas, long-term conservation of the device and disposables must be ensured upstream to the place of use, even in adverse conditions. The device's disposables should all have very little environmental impact because low-resource areas often have subpar waste-management systems (Donders 2011).

Many of these difficulties have already been taken into consideration as current biomedical R&D works to produce highly integrated, portable

biosensors that are very user-friendly and utilize very little reagent. This is enabled by multiple factors: the detection system's component parts being smaller (Donders 2011) (Farré et al. 2009), the optimized micro-structuring of the transducer (e.g., nano-wires (Bhushan 2012)), nano-pores (French et al. 2011), nano-particles (Gerke et al. 2019), the micro spotting of the sensitive element (Gupta and Kakkar 2020), and the integration within the transporter (e.g., with low-volume-consumption microfluidics (Mufamadi and Sekhejane 2017). Additionally, field analysis through wireless communication between remote sites and centralized labs can be made possible by the recent widespread use of smartphones as imagers (Saini et al. 2019). The possible flexibility of biosensors with regard to their analytical capabilities is another important technical characteristic. For example, a biosensor that can test for multiple diseases simultaneously or one of numerous alternatives would unquestionably be useful when the goal is to identify an infectious virus in the blood. These days, numerous multiplexing methods that enable the simultaneous quantification of hundreds of biomarkers make this adaptability possible (Sha et al. 2017).

However, there is a disadvantage to all of these options: the current trend in R&D is to strive toward complex and divergent applications to show the entire spectrum of uses, which slows down development, diverts attention from industrial scalability, and delays product deployment. If developing countries are to benefit from biosensors, striking a balance between the pursuit of the best technological solution and the most suitable for underdeveloped environments with urgent medical needs is imperative; addressing particular and urgent needs would surely be crucial for successful deployment (Sha et al. 2017).

However, it appears that limiting the steps in the biosensing workflow are often upstream and downstream from the biosensor application itself, even for devices that fulfil technological maturity levels. When suggesting solutions for underdeveloped nations, the difficulties associated with sample collecting and storage are frequently overlooked on the upstream side. In fact, the activity of a professional operator and/or the usage of specific equipment are frequently required for the proper execution of the sample collection and preparation for blood collection (Donders 2011).

Furthermore, materials that are not prepared and examined immediately must nearly always be stored under strictly regulated circumstances. Using biosensors does not, however, negate the need for a doctor's guidance downstream. A doctor will still evaluate the results, connecting them to other symptoms and prescribing medication or requesting additional testing. Biosensors alone cannot make some diagnoses, and false positives and negatives should never be ruled out (Bhushan 2012).

Thus, in tandem with their distribution, a network of qualified personnel should be established who are suited to handle and use the

biosensor product at a degree of complexity appropriate for handling samples and selecting appropriate follow-up therapies. If this is not considered early enough in the implementation phase, remote areas run the potential of being overrun with 'gadget-biosensors' before the skills required to manage them are developed. This may result in pollution, squandered gadgets, and incorrect diagnoses, among other things (Bhushan 2012).

To more effectively target pertinent and workable applications, these aspects should be taken into account as soon as feasible, even if they are not directly within the purview of the associated companies and researchers. In contrast, governments and overseeing bodies have a crucial role to play in setting up all the necessary financial and material resources as well as acting as regulators and sources of funding (Gupta and Kakkar 2020).

Tackling Financing and Regulations

Even in affluent nations, biosensing technologies are still having difficulty making the transition from labs to practical applications, despite their promising future. A notable instance that has garnered significant attention in the last ten years is the genome sequencing experiment (Stevenson et al. 2019), the cost of which decreased from 100 M$/subject to 1 k$/subject in less than fifteen years (Verma and Singh 2005). This demonstrates how the private sector can lower the price of methods to cater to particular uses. But even when the cost of the underlying technology is reduced to a minimum, this frequently leads to products that are too expensive in low-resource environments. This happens because the primary strategy for cutting costs is the ongoing improvement of high-tech processes, as biosensors in industrialized nations are typically built to achieve commercial profitability. On the other hand, rich environments are rarely the ones that choose to invest in low-cost breakthrough technologies.

Cheap materials can be used to enable such an approach (Vilariño et al. 2009) and open-source components (Karim 2022, Sergeev et al. 2007, Rogers and Williams 1995, Ravizza et al. 2019, Migliozzi and Guibentif 2018). For instance, free designs for hardware such as microfluidic modules (Polshettiwar et al. 2021) and microcontrollers (Srinivasan and Tung 2015) may help in creating a cheap transporters. Free schemes and procedures are also available for high-resolution optical detection (Alocilja and Radke 2003) and image-processing (Pereira Da Silva Neves et al. 2018) and can come in rather handy while designing the detection system. This new development methodology, which begins with open-source building blocks, has the potential to dramatically reduce the cost of solutions that are usually highly customized. But most stakeholders are not always amenable to such a community-driven approach because they

have a financial incentive in keeping their know-how safe (Polshettiwar et al. 2021).

Test costs, however, must be taken into account in conjunction with other crucial variables, such as disease prevalence, treatment costs, maltreatment costs, and throughput. In fact, improving the accuracy and turnaround time of current diagnostic tests can decrease the number of unnecessary presumptive treatments and more effectively utilize the ones that are required, increasing the net benefit in resource-constrained environments. This is why cost-effectiveness for diagnostic tests takes this into account. In order to determine the estimated cost of a diagnostic gadget, one needs study the policy makers' assessment of a disability-adjusted life-year (DALY) in certain nations. As a result, a reduced price does not always translate into a better deal (Chadha et al. 2022, Madrid et al. 2022, Shukla and Suneetha 2017, Bhattarai and Hameed 2020, Siontorou and Georgopoulos 2021, Singh et al. 2021).

The US government is providing a significant amount of funding, primarily for disease testing motivated by biodefense concerns (Tapuhi and Venter 1996). However, the resources provided by national programs, non-profits, international agencies, and donations would likely not be sufficient to meet the needs for both biosensor device research and commercialization. One other source of funding might come from the commercial sector's own subversion of the early biosensor adoption in test zones. This could show how useful the gadgets are and open the door to more funding (Andryukov et al. 2020).

Finally, in addition to financial constraints, stringent international healthcare standards provide significant regulatory obstacles to the widespread adoption of biosensors in developing nations. In a highly competitive climate, companies under constant pressure to secure the certifications necessary for the uptake of their products (Pejcic et al. 2006). For example, start-ups trying to capitalize on current technology to create diagnostic tools based on those genes or molecules face increasing costs due to the licencing of genes and chemicals. Furthermore, even while labs frequently introduce exciting new technologies, it might be challenging to achieve strong reproducibility of results in the final prototype, which could hinder meeting the requirements necessary to meet regulatory requirements. Furthermore, other challenges including delays, inconsistent practices, and unpredictable medical agencies may arise independently of the market and local decision makers, even when all the resources and efforts are put in place for this aim (Hussain et al. 2022). Moreover, the lack of established standards for assessing diagnostic tests in developing nations makes it challenging for the government and healthcare system to choose which alternative tests to acquire. Additionally, any interventions (such as treatment or additional testing) made after a biosensor test must

be legally attributed to the habilitated individual. Even in cases when the technological and financial prerequisites are satisfied, the deployment of biosensors in low-resource environments necessitates the establishment of a network of trained individuals as well as customized frameworks and laws (Qu et al. 2020).

Conclusion

Biosensor technology has the potential to bring about a paradigm shift in the advancement, maintenance, and preservation of human health which is crucial for the fulfilment of human rights. By monitoring different aspects of the environment and biodiversity, biosensors show promise and can help achieve some of the Sustainable Development Goals (SDGs) set forth by the United Nations for 2030. Despite all the assurances, there are still certain issues and obstacles related to law, regulations, and ethics that need to be addressed. Many national and international organizations that have the authority to oversee the development of scientific and technological applications and their effective regulation have already produced a number of general regulatory tools that are either process- or product-based and can be applied to the field of biosensors, even though there aren't many that are made specifically for this purpose.

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8

Exploration of the Growing Potentials of Nanosensor Usage

Future Perspectives and The Way Forward

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Introduction

Nanosensors are specialized sensing devices, offering the combined benefits of nanotechnology and biosensing. Conventional strategies often lack specificity and sensitivity, and are slowly being replaced by nanosensors produced from a variety of nanomaterials, each based on a different operating principle and offering unique benefits. For the sake of convenience, the applications of nanosensors have been evaluated under three broad headings in this chapter: with reference to the pharmaceutical industry and clinical developments, followed by the food industry, as well as agricultural and environmental applications.

Nanosensors have gained significant traction in the healthcare industry over the last decade. As the prevalence of infectious diseases across the globe continues to grow, there is a need to explore novel therapeutic and diagnostic interventions to reduce the growing pressure on healthcare

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systems (Deng et al. 2021). In addition to applications in the healthcare sector, nanosensors have been employed in a variety of industries and have yielded promising results. The applications of nanosensors continued to expand exponentially, owing to their ability to monitor physical and chemical changes in areas that are otherwise difficult to access, such as events on a cellular and nanoscopic level (Adam and Gopinath 2022).

Within physiological systems, nanosensors have been observed to directly interact with a variety of biological molecules, even at very low concentrations. This encompasses detection using a variety of techniques, some of which include fluorescence, electrochemical and thermal detection (Arndt et al. 2020). Following the unprecedented damage caused by the COVID-19 pandemic, the need to develop newer technologies and improve pre-existing methods was felt. Therefore, since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), significant advances have been made in nanosensor technology. These include diagnostic methods, as well as treatment strategies for other opportunistic infections (Singh et al. 2021). An interesting application in recent times has been the emergence of nanosensor usage in wearables and health-monitoring technologies, especially using alternate energy sources such as self-powered nanosensors, keeping in mind the focus on sustainability and cost-benefit analysis (Zheng et al. 2023).

Nanotechnological advancement has ushered in progress in the agricultural and food industry, owing to a myriad of benefits offered, such as an improved quality of products, safer agricultural practices and more stringent process monitoring (He et al. 2019). The rapid emergence of newer techniques to check microbial contamination, as well as those enhancing the integrity of packaging and storage has helped boost the output and reduce wastage, prompting an improvement of global nutritional parameters. In addition to this, nanosensors have been used in the targeted delivery of antimicrobial agents to plants, reducing disease occurrence and ensuring a healthier crop yield (Hamad et al. 2018). As we move forward, it is expected that there shall be an increased number of avenues where nanosensors may be employed, and the rationale for their usage is highlighted in this chapter.

However, in order to fully reap the benefits of these technologies and maximize outcomes, several challenges and limitations must be prudently addressed. These include biocompatibility and stability challenges and raising the need for selection of specialized nanomaterials, which may increase production costs, and in turn, increase the cost for the end-user (Yang and Duncan 2021). In addition to this, most of the proposed applications find limited usage on an industrial or clinical scale, owing to scale-up and production challenges. It is also essential to cultivate an understanding of other challenges posed by nanosensor usage, such as nanotoxicity and increased predisposition to certain disease conditions on

prolonged usage, such as cancer (Ali et al. 2021). Most nanosensor systems require specialized, multi-channel detecting systems, thus limiting practical applications. These challenges must be effectively addressed in the future, along with the establishment of a well-structured regulatory framework for standardization and approval. In addition to this, undertaking of education with respect to usage and specific applications in disease management by public health organizations must also be highlighted, in order to outline the utilization and possible challenges involving the operation of these technologies across different demographics.

Alongside discussing a variety of applications across different industries, the authors have also addressed the advent of artificial intelligence (AI) and the usage of cloud-based technologies for diagnostic purposes and personal health mapping. In addition to the uses in the healthcare industry, a discussion on technological systems for collection and sharing of data generated from nanosensor usage in the food and agricultural industry, as well as environmental monitoring, has also been provided.

Applications in the Food Industry

Nanosensors have been widely used in the food industry, chiefly to monitor the level of pathogens, prolong shelf-life and for quality assurance purposes, in order to meet regulatory requirements. This section offers a comprehensive overview of the applications of nanosensors at various touch-points, ranging from the manufacturing and packaging of foodstuffs to monitoring their quality over extended periods of time.

Bacterial biofilm formation has been a challenge for the food industry, owing to the risk of pathogenic contamination due to unchecked proliferation (Liu et al. 2023). Optical nanosensors have been utilized as an effective tool for biofilm detection, and various modifications, such as quantum-dot (QD) based nanosensors, magnetic nanoparticles-based devices. Those incorporating noble metals such as gold and silver have been explored for the benefits offered. Research advancements have enabled the usage of a variety of biomaterials in the fabrication of nanosensors, to address key challenges such as the toxicity and inhibitory effects of biofilms. This strategy offers a distinct advantage over conventional approaches. Another key application is the detection of bacterial quorum sensing, which may also be monitored in aquaculture to control bacterial multiplication (Zhang and Ye 2014). However, a major point that must be addressed in the future is the biocompatibility and reproducibility of these nanosensors (Pu et al. 2021). There is a scope for further development in terms of the design and diversity of these devices, to broaden the scope of detection to a greater variety of microbes.

In addition to this, gold nanoparticle-based optical nanosensors have been employed in the food industry for ensuring the maintenance of the highest standards of health, and preservation of freshness. Key advantages include ease of visual detection and enhanced sensitivity in pathogen recognition. However, the synthesis of optical nanosensors is a cost intensive process. As cost-effective alternatives continue to be explored, including electrochemical sensors, the scope of usage of these nanosensors may be extended to the detection of heavy metals, pesticides, as well as additives in foodstuffs. This, in turn, may be used for the management of diseases resulting from uncontrolled concentrations of these agents, thereby enhancing health outcomes and averting the risks associated with the consumption of contaminated food (Anh et al. 2022).

A growing challenge in the food industry is unchecked wastage. This primarily results from microbial contamination, thereby decreasing the viability of products and increasing the incidence of disease, and prompting wastage due to such articles being discarded. Nanosensors have been used as intelligent technology tools for detecting food spoilage as well as improving nutritional value and elongating shelf-life. In addition to this, nanosensors have also gained attention in the packaging industry. They have been utilized in intelligent packaging systems, to provide an indication of product quality. Intelligent packaging systems also provide an insight into the pH, temperature and freshness of packaged materials, and have found applications in health, food and household products (Ehsani et al. 2022).

While applications in food packaging have been observed to be relatively safe, there is a need to carry out a greater number of studies to demonstrate the inclusion of these agents in consumables (Nile et al. 2020). Their effects on key biological processes such as DNA replication and the cell cycle must be evaluated, in addition to instituting a greater number of regulatory norms to monitor their safety and efficacy (Yang and Duncan 2021).

Another interesting development has been the usage of lipid-based biosensors, in the food industry. Owing to their biocompatibility and analogous nature to the physiological lipid bilayer, they have been used for the detection of a variety of biomolecules (Nikoleli 2020). Formulators must focus on lowering the cost of production and reducing the bulkiness of these devices to the greatest extent possible, in order to present them as a comparable detection technique to already established chromatographic methods of analysis.

As the focus on environmental sustainability continues to grow, there is a need to implement more viable production processes. Nanosensors have been utilized to detect environmental changes such as those in temperature, humidity, and for identifying biomarkers secreted by microorganisms, which may indicate spoilage (Jia et al. 2023). They offer

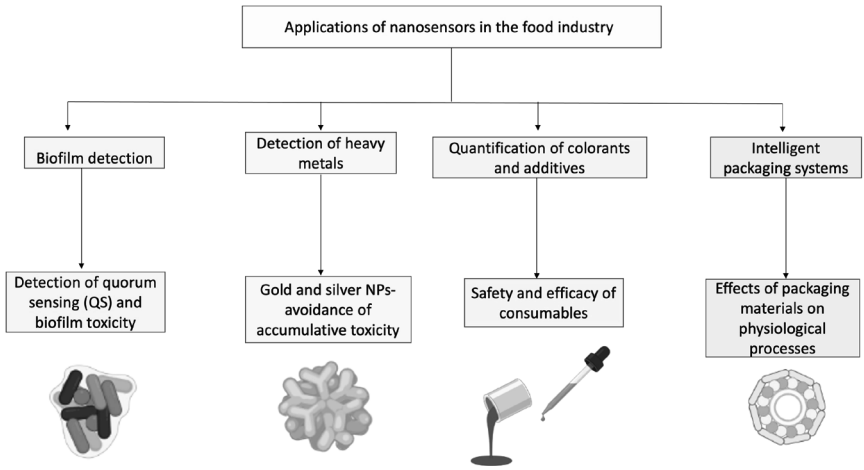
Applications of nanosensors in the food industry
Biofilm detection
Detection of heavy metals
Quantification of colorants and additives
Intelligent packaging systems
Detection of quorum sensing (QS) and biofilm toxicity
Gold and silver NPs-avoidance of accumulative toxicity
Safety and efficacy of consumables
Effects of packaging materials on physiological processes

Fig. 1. Overview of the applications of nanosensors in the food industry (Created with BioRender.com). ⏎

advantages over traditional methods, due to their ability for more specific detection, even at low concentrations and faster analysis. In addition to this, future perspectives include the usage of nanosensors by consumers as opposed to limiting their usage to laboratory settings, in order to monitor the quality of food in real time.

However, the utilization of nanotechnology in food processing is hindered by several limitations. These include an increased predisposition to cancer, possible toxicity and safety concerns, as well as damage to organ systems such as the digestive system (Thiruvengadam et al. 2018). While their applications are promising and have attracted significant attention over the last few years, there is a need to undertake more thorough analysis of their working and potential safety concerns, before amplifying their utilization. Figure 1 offers an overview of the current and future applications of nanosensors in the food industry.

Pharmaceutical and Clinical Applications

The quest for greater sensitivity and early detection of pathologies has driven research and innovation in biosensor technology. Nanosensors based on different operating principles, such as optical, mechanical and magnetic detection to name a few, are being constantly modified to improve sensitivity, and detect biomarkers at previously impossible concentrations. This is chiefly facilitated by improved signal and target amplification (Swierczewska et al. 2012). A recent example of such innovation is the increased adoption of integrated biosensors, for point-of-care diagnostics and improved patient outcomes (Dincer et al. 2022).

Microneedles have been explored as a minimally invasive technique for the delivery of insulin for the management of diabetes, owing to the relative ease of usage, minimal damage to tissues and cost efficiency (Zahoor et al. 2022). Progress in research has enabled the incorporation of Silicon-nanowire field-effect transistors (SiNW-FETs) nanosensors onto microneedles. The key advantages offered by this innovation includes the detection and quantification of multiple key metabolites, without the need for extraction and clinical estimation. Continuous monitoring may be undertaken, which serves as an effective, personalized tool for diabetes management (Heifler et al. 2021). In the future, a greater number of clinical biomarkers may be detected using this technology, broadening the scope to a greater number of disease conditions. Such a personalized monitoring device could potentially reduce the ever-increasing pressure on the healthcare infrastructure, and assist easy delivery of agents and timely monitoring.

Quantum dot (QD) based nanosensors have been employed for genetic analysis, including DNA mapping and mRNA assays, as well as monitoring enzymatic activity. They enable colorimetric detection of oligonucleotide sequences, as well as pathogenic detection by facilitating the mapping of multiple gene sequences simultaneously (Zhang et al. 2012). Moving forward, these QD based nanosensors may be utilized clinically for the detection of various diseases, owing to a low detection limit and high sensitivity. As advancements continue, this method may be harnessed as a hyphenated technique, when combined with fluorescence resonance energy transfer (FRET), opening up newer possibilities for the detection of viruses and small biological molecules (Hu et al. 2017).

In a quest to devise non-invasive diagnostic and imaging techniques for cancer, magnetic nanoparticles have been incorporated into nanosensors. These magnetic nanosensors have also been employed in drug delivery, and have gained significant clinical interest. Owing to their large surface area, stability and target specificity, the scope of their application has been extended to a variety of conditions, including genetic diseases (Laraib et al. 2022). However, there are several challenges that need to be addressed before the tranformation from research to clinical settings is made. These include ensuring biocompatibility of the nanoparticles incorporated, non-toxicity, as well as appropriate control of their size based on their application. The distribution of the dose within living systems as well as localized inflammation may be monitored, to assess the safety profile of these agents (Doswald et al. 2019).

Significant progress has been made in the design of these nanosensors, a key example being the incorporation of low-dimensional materials to facilitate targeted glucose monitoring. The key advantages offered include the provision of a larger surface area, greater sensitivity as well as improved stability (Xu et al. 2021). This highlights the need for exploring

alternatives to nanomaterials currently in use, in order to improve the performance and utility of these devices. Nanosensors are poised to grow in the diagnostics and imaging space, owing to their relatively low costs, greater sensitivity and quicker, real-time monitoring, in comparison with conventional analytical techniques such as spectroscopy (Sharma Pankaj et al. 2021).

Siderophores, which are biomolecules secreted by certain microorganisms to enhance the uptake of iron, have been employed in biosensors for diagnostic applications. In addition to elemental detection, they serve other applications, such as the detection of antibiotics, microorganisms and peptides (Khasheii et al. 2021). The key advantage offered is the sensitivity possessed by these systems, which is widely employed in diagnostics. Moving forward, avenues for combining these biosensors with established nanosensor technologies may be explored. While the process of isolation of these biomolecules remains a challenge, more focused research could facilitate the development of more efficient characterization and isolation techniques. As our understanding of these systems continues to grow, opportunities for usage in cancer management and immunoassays by conjugation with aptamers may offer promising clinical results (Nosrati et al. 2018).

Nanosensors may be employed in the detection and management of diseases wherein timely intervention is a critical factor. A key diagnostic application of nanosensors lies in the detection of sepsis. While its complex aetiology poses a challenge to the development of diagnostic and therapeutic methods, nanosensors have been employed to enable early detection and suitable therapeutic intervention (Alba-Patiño et al. 2022). Nanosensors based on various technologies, including electrochemical and magnetic systems, have not only enabled the detection of key diagnostic biomarkers, but have also facilitated the management of drug resistance arising from over-usage of antibiotics (Pant et al. 2021). Owing to the intricate biochemical signaling, targeting one specific pathway may be challenging. Further research and subsequent translation to clinical usage may eventually enable a more specific approach, as opposed to targeting multiple molecular pathways.

The evolution of nanotechnology has paved the way for the applications of Surface-enhanced Raman spectroscopy (SERS) nanosensors in mapping cellular microenvironments, detection of gases such as carbon monoxide and nitric oxide, as well as reactive oxygen species (ROS) (Skinner et al. 2021). The quantification and control of these parameters may be utilized in the management of diseases arising from cellular dysfunction or an increased oxidative load. However, a key challenge remains in the commercialization and reproducibility of these technologies (Jahn et al. 2020). As we analyze future perspectives, there is a need to develop better

sampling techniques, as well as assessing cost-effective nanomaterials to improve accessibility.

The presence of excessive nitric oxide in the environment, beyond a threshold value, may increase the risk of development of respiratory disorders, such as emphysema (Yatera and Mukae 2022). Harnessing metalloporphyrin-based nanosensors has yielded several benefits, such as sensitivity of detection, short recovery time of the biosensor following contamination, and selectivity towards specific gaseous components (Ostovan and Naghavi 2022).

The emergence of the SARS-CoV-2 virus and subsequently the COVID-19 pandemic served as a trigger for innovation and applications of previously developed concepts, expanding the horizon of the applications of nanosensors in healthcare. Some notable advancements include vitamin C-loaded nanosensors to assist recovery and boosting of immunity (Zhao et al. 2021) and biosensors embedded into personal protective equipment (PPE) such as masks (Tharayil et al. 2021), to name a few. Nanosensors have also been utilized for the detection of enzymes indicative of DNA damage, offering improved sensitivity and ease over conventional assay methods, and assisting in the selection of clinical strategies (Li et al. 2019). Figure 2 provides a representation of the clinical applications of nanosensors.

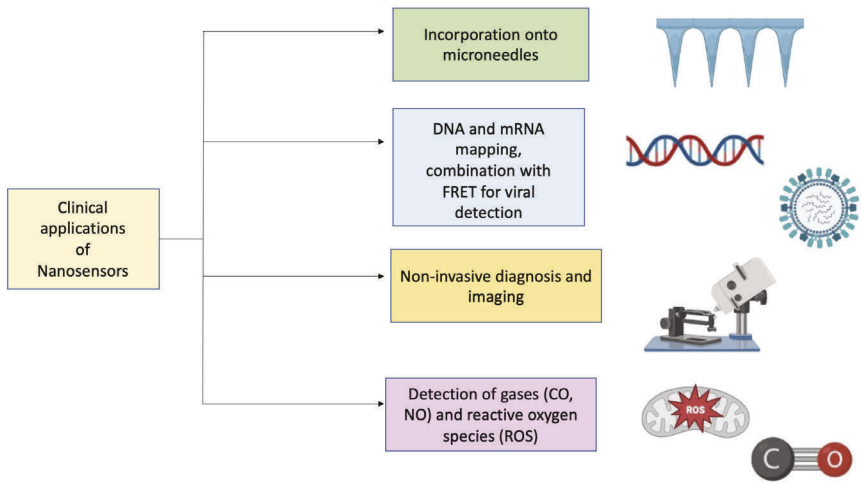
Clinical applications of Nanosensors
Incorporation onto microneedles
DNA and mRNA mapping, combination with FRET for viral detection
Non-invasive diagnosis and imaging
Detection of gases (CO, NO) and reactive oxygen species (ROS)
ROS
C
O

Fig. 2. Clinical applications of Nanosensors (Created with BioRender.com).

Agricultural and Environmental Applications

In order to enhance agricultural yield, nanosensors have been used to improve the functioning of chloroplasts. By facilitating DNA delivery via nanosensors, better crop yields may be achieved. The key advantages

offered includes an improved stress response and optimal utilization of natural resources (Dhiman et al. 2021). However, moving forward, there are several lacunae that must be addressed. There is a pressing need to craft an appropriate strategy for the delivery of these nanosensors to cell organelles, owing to an incomplete understanding of the intricate interaction mechanisms involved between the nanosensors and chloroplasts. Additionally, future perspectives would include testing the scalability of these devices from lab settings to agricultural fields (Newkirk et al. 2021). In order to ensure widespread application, there is also a need to understand the functioning of the physiological processes of different plant species, as well as the implications of nanosensor usage.

DNA-based nanosensors have been employed for the detection and quantification of a variety of environmental pollutants, such as antibiotics, heavy metals and pesticides, through the recognition of specific genetic elements (Ghormade et al. 2011). They offer a variety of advantages over traditional methods, owing to their improved sensitivity, possibility of real-time analysis and relatively easy operation. Future implications encompass the detection of a variety of viruses, owing to the increased prevalence of viral diseases. The coupling of nanosensors with digital systems may boost theiryfavorability in markets across the globe, with potentials of remote usage being explored (Kumar and Guleria 2020).

Recently, the emergence of plant nanoscience has opened up avenues for the applications of nanotechnology in agricultural settings. As our understanding of the metabolic pathways of plants as well as the pathogenesis of diseases affecting crop output continues to increase, nanosensors may be increasingly employed to improve harvests (Zhang et al. 2022). Owing to the widespread availability of zinc, and beneficial elemental properties such as fluorescence and electron generation, it has been utilized in the designing of nanosensors for the management of plant diseases. The key objective is the delivery of antimicrobial agents to check the growth and proliferation of plant pathogens (Sharma Pramila et al. 2021, Silva et al. 2022). Notwithstanding the benefits offered, the implications of zinc entering the food chain and implications of its presence in biological systems need to be understood to a greater degree, before scaling up production (Kalia et al. 2020).

Intervention of Artificial Intelligence (AI)

The advent of artificial intelligence (AI) has aided the enhancement of the functioning and applications of nanosensors, chiefly in clinical settings. Following the outbreak of the COVID-19 pandemic, smart diagnostic techniques using nanosensors have been gaining popularity. This includes the usage of cloud-based technology, for diagnosis and recording of therapeutic interventions (Hosseinifard et al. 2021). Community-acquired

pneumonia (CAP) proved to be a challenge during the pandemic, increasing the load on already collapsing healthcare systems. The development of nanosensors monitoring host protease activity and assisting diagnosis through urinary output was an interesting development (Anahtar et al. 2022). AI may be harnessed to map the therapeutic outcomes across demographics, and generate clinical data that may be accessed with ease across the globe.

While the pandemic exposed areas of improvement with respect to the diagnosis of diseases, it also prompted the development of robust systems for environmental monitoring to check the proliferation of disease-causing pathogens. Digital tools were used for the assessment of wastewater, employing biosensing platforms. Microfluidic chips were employed for colorimetric detection of the virus in sewage samples, integrating machine learning. While the technology is still in its developmental stages, it is proposed that smartphones connected by a cloud network may be utilized for local sharing of clinical results and disease mapping (Mahmoudi et al. 2022).

As we continue to progress into the age of AI and Internet of things (IoTs), noteworthy developments have been made in the arena of wearable health technologies. They have been used to monitor key physiological parameters, such as blood pressure. Thesesnano systems offer a host of advantages, such as reliability in measurement, diversity in construction and cost-efficiency (Venugopal et al. 2021).

Another interesting advancement has been the development of a nanosensor relying on machine learning for the detection of methanol in alcoholic beverages. Although chromatographic techniques exist for this purpose, they are not cost- and time-effective. The usage of a gas nanosensor working on a thermal gradient has been proposed, and it has demonstrated efficacy in a variety of humidity conditions. This technology may be utilized clinically for the diagnosis of alcohol poisoning (Tonezzer et al. 2022).

With respect to the food industry, wireless technologies have been developed for the detection of undesirable compounds in meat products. An example of this is the usage of a wireless nanosensor for the quantification of terbutaline in meat products. It yielded comparable efficacy with traditional nanosensors, as well as a good recovery rate. This indicates potentials for further development and commercialization of such smart system based technologies (Ge et al. 2022).

While newer technologies continue to emerge, it is essential to acknowledge the role played by AI in serving as a bridging link between the present and future of nanosensors. Continued research would enable the development of more cost-effective technological solutions, as well as aid the expansion of the scope of applications of these improved nanosensors.

The convergence of AI and nanosensors could potentiallyecatalyze a vast number of scientific breakthroughs, across various disciplines.

Conclusion

The importance and relevance of nanosensors has already been established, outlining the scope of their usage across several industries. These specialized devices offer a range of benefits over conventional delivery and imaging techniques, and continuous improvement has been prompted in the backdrop of newly emerging diseases, both in humans and plants.

Before their potential is fully realized, there is a need to undertake focused effort through clinical research, in order to develop a holistic view of these devices, and translatability across paradigms. Nanosensors offer several advantages, however, their translation to clinical and industrial practice remains unfulfilled to a great extent. There is a need to conduct a greater number of clinical studies to obtain a record of their toxicological profiles and efficacy, preceded by in-silico screening and other preclinical studies, to establish their safety before introduction into living systems. There have been observations made with respect to the onset of nanotoxicity and low systemic clearance following usage, and these challenges must be suitably addressed.

In addition to understanding the current scenario of their usage, it is essential to cultivate an understanding of future perspectives and possible advancements to their design and construction, which may yield improved outcomes. One such advancement is the linkage of AI with nanosensors, to broaden the scope of application and facilitate easier tracking and monitoring of results. This is essential to facilitate a greater degree of cooperation across the globe and sharing of relevant data to tackle challenges faced by different industries wherein these devices find their applications. Through this chapter, the authors have aimed to offer a contemporary understanding of applications of nanosensors across three broad industries, backed by a thorough discussion of the challenges that must be addressed, before full-fledged usage. It is hoped that the timely addressal of these pitfalls would pave the way for greater applications in the future, improved market access and cost-effectiveness, as well as a greater range of benefits to the end users.

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